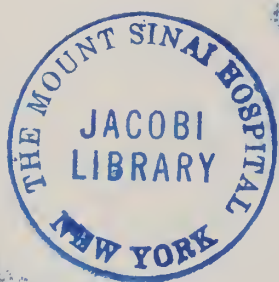




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CONTENTS OF VOLUME XIX

NUMBER 1, MAY-JUNE, 1952

	PAGE
FOREWORD. <i>Joseph H. Globus, M.D.</i>	ix
ERNST PETER PICK, THE SCIENTIST. <i>Otto Loewi</i>	xii
TRIBUTE TO A LOST WORLD. <i>George Bachr, M.D.</i>	xiv
ON THE ACTION OF FLUORIDE ON THE HEART OF RANA PIPIENS. PRELIMINARY NOTE. <i>O. Loewi</i>	1
SUSCEPTIBILITY TO CONVULSIONS IN RELATION TO AGE. <i>Alfred Froehlich, M.D.</i>	4
AMYLOIDOSIS IN MULTIPLE MYELOMA. PROGRESS NOTED IN 50 YEARS OF PERSONAL OBSERVATION. <i>A. Magnus-Levy, M.D.</i>	8
DIE WIRKUNG ELEKTRISCHER HYPOTHALAMUSREIZUNG AUF DEN EXPERIMENTELL ERZEUGTEN BRONCHIALMUSKELKRAMPF. <i>F. v. Brücke, F. Kaindl, H. Mayer, und A. Neumayr</i>	10
DISSEMINATED LUPUS ERYTHEMATOSUS. (MALIGNANT LUPUS ERYTHEMATOSUS (GOLDSMITH-BEAR)). SEINE GESCHICHTE—VERSUCH EINER BEGRIFFSBESTIMMUNG. <i>L. Arzt</i>	19
UEBER DIE NEUROGENE APPENDICOPATHIE. <i>H. Chiari</i>	30
ÜBER AUTOMATIK UND DEREN GRENZEN. <i>A. Durig</i>	38
GEWÖHNUNGSVERSUCHE AN FIBROBLASTENKULTUREN. <i>W. Heubner, M. Albrecht, E. Barocke, und H. Kewitz</i>	47
ANTIACCELERATOR CARDIAC AGENTS. <i>Otto Kraye, M.D.</i>	53
MODIFICATIONS OF THE HEART SOUNDS IN BUNDLE BRANCH BLOCK. <i>Stephen Contro, M.D. and Aldo A. Luisada, M.D.</i>	70
THE TRANSFER OF DRUGS INTO THE MILK. <i>Hans Mautner, M.D.</i>	83
EFFECT OF EXCESSIVE DOSES OF CORTISONE, ACTH AND PROLACTIN IN PREGNANT AND NURSING MICE. <i>Susi Glaubaeh, M.D.</i>	88
THE CHANGING PATTERN OF INFECTIOUS PROCESSES UNDER THE INFLUENCE OF CORTISONE. <i>William Antopol, M.D. and Howard Quittner, M.D.</i>	91
HUMAN AND EXPERIMENTAL ARTERIOSCLEROSIS. <i>David Lehr, M.D. and Jacob Churg, M.D.</i>	106
ZUR FRAGE DER ÜBERTRAGUNG SENSIBLER IMPULSE IN RÜCKENMARK DES FROSCHES. <i>Hans F. Häusler und Heinz Sterz</i>	121
INDICATIONS OF BED REST, PARTICULARLY IN THE AGED. <i>Albert Mueller-Deham, M.D.</i>	131
EXPERIMENTAL STUDIES ON RENAL CIRCULATION. <i>E. Rothlin and A. Cerletti</i>	138
THE EFFECT OF HISTAMINE ON AN ISOLATED SYMPATHETIC GANGLION. <i>H. Konzett</i>	149
ÜBER ANGRIFFSPUNKT UND WIRKUNGSWEISE MORPHINÄHNLICH WIRKENDER ANALGETIKA. <i>O. Schaumann</i>	154
"NICOTINIC ACTIVITY" AND THE PROBLEM OF PHARMACOLOGIC SELECTIVITY. <i>S. Loewe</i>	160

19766

RESISTANCE TO GRAFTING WITH LYMPHOSARCOMA CELLS IN RATS INJECTED WITH HOMOLOGOUS LYMPHOID CELLS. <i>H. C. Stoerk, Tatiana Budzilorich, and T. C. Biclinski.</i>	169
THE MODE OF ACTION OF ANTIBIOTICS: PENICILLIN AND STREPTOMYCIN. <i>W. W. Umbreit and E. L. Oginsky.</i>	175
EINFLUSS DES DESOXYCORTICOSTERONS UND ANDERER STERINE AUF DIE ZELLMEMBRANDURCHLÄSSIGKEIT DER GELENKKAPSEL. <i>P. Stern.</i>	185
DIE BEDEUTUNG DER EXPERIMENTELLEN PHARMAKOLOGIE FÜR DIE NEUROLOGIE UND PSYCHIATRIE. <i>Ottokar Arnold und Hans Hoff.</i>	191
FIXATION OF COMPLEMENT WITH THE PURIFIED FACTOR IN MOUSE MILK CONNECTED WITH MAMMARY CARCINOMA. <i>Michael Heidelberger, Ph.D., Myron A. Leon, Samuel Graff, Ph.D., and C. D. Haagensen, M.D.</i>	210
ISOTOPICALLY LABELED NIRVANOL. <i>Harry Sabotka, Ph.D. and F. E. Stynler, Ph.D.</i>	212
EFFECT OF SOME REAGENTS ON THE FLUORESCENCE OF STILBAMIDINE AND 2 OH-HYDROXYSTILBAMIDINE IN VITRO. <i>F. Lieben, Ph.D.</i>	217
THE INFLUENCE OF EXPERIMENTAL HYDRONEPHROSIS AND OF SEVERAL AMINO ACIDS ON THE NEPHROTOXIC ACTION OF DL-ETHIONINE. <i>M. Wachstein and E. Meisel.</i>	221
UPTAKE OF P ³² IN SEMINAL VESICLES OF CASTRATE RATS AFTER TREATMENT WITH TESTOSTERONE PROPIONATE. <i>Walter Fleischman, M.D., Ph.D. and Susan Kann Fleischmann, Ph.D. With the technical assistance of Ruth S. Raper, M.A. and Ida L. Gustus.</i>	228
THE INTEGRATED ROLE OF CATECHOLAMINES, MINERALOCORTICOIDS AND SODIUM IN HYPER- AND HYPOTENSION. (A WORKING HYPOTHESIS). <i>W. Raab, M.D.</i>	233
PHYSIOLOGIC AND PATHOLOGIC ALLERGY. <i>Bela Schick, M.D.</i>	240
THE RELATIONSHIP OF XANTHOMA JUVENILE TO SYSTEMIC RETICULOENDOTHELIOSIS. <i>Paul Freud, M.D.</i>	243
PROBLEMS IN JUVENILE DIABETES MELLITUS. <i>Richard Wagner, M.D.</i>	249
SERUM AND HEPATIC ENZYMES IN EXPERIMENTAL LIVER DAMAGE. <i>Hans Popper, M.D., Ph.D., Dieter Koch-Weser, M.D., and Jesus De La Hueraga, M.D.</i>	256
BLOOD PRESSURES OF CHRONIC HYPERTENSIVE DOGS SURVIVING BILATERAL NEPHRECTOMY. <i>B. S. Oppenheimer, M.D., Stephen S. Rosenak, M.D., and Gordon D. Oppenheimer, M.D.</i>	266
ON THE INCIDENCE OF CARCINOMA IN CHRONIC ULCERATIVE COLITIS. <i>Sadao Otani, M.D. and Isidore Snapper, M.D.</i>	275
CORONARY ATHEROSCLEROSIS IN THE YOUNG: CLINICAL AND PATHOLOGIC OBSERVATIONS. <i>David Adlersberg, M.D. and Frederick G. Zak, M.D.</i>	289
PROBLEMS IN THE MANAGEMENT OF REFRACTORY HEART FAILURE. <i>Charles K. Friedberg, M.D. and Mark Halpern, M.D.</i>	303
ACUTE GASTRIC DILATATION. <i>Ernest Gold, M.D.</i>	310
SOME OBSERVATIONS ON THE NUCLEIC ACIDS. <i>Samuel Graff, Ph.D.</i>	313
THE USE OF DIBENAMINE IN PHEOCHROMOCYTOMA AND DETECTION OF PRESSOR ACTIVITY OF THE PLASMA BY BIO-ASSAY. <i>Henry Haimovici, M.D.</i>	320

	PAGE
THE ECCRINOLOGICAL CLASSIFICATION OF GASTRIC MUCUS. <i>Franklin Hollander, Ph.D.</i>	328
THE INFLUENCE OF TOXIC AGENTS ON THE FEMALE GENITAL ORGANS. A BRIEF REVIEW. <i>Josef Novak, M.D.</i>	333
THE EFFECT OF THIOUREA ON MITOSIS IN RAT LIVERS DAMAGED BY CARBON TETRACHLORIDE. <i>M. Rachmilewitz and A. Rosin</i>	339
LABORATORY AIDS IN THE DIAGNOSIS OF HYPERTHYROIDISM. <i>Solomon Silver and Sergei Feitelberg</i>	345
PLUMBISM IN CHILDREN. <i>Frederick G. Zak, M.D. and William E. Finkelstein, M.D.</i>	352
ABSTRACTS.....	359
INDEX TO NUMBER 1, VOLUME NINETEEN.....	375

NUMBER 2, JULY-AUGUST, 1952

	PAGE
OTOLOGY: ITS PRESENT STATUS. <i>Julius Lempert, M.D.</i>	381
THE WILLIAM HENRY WELSH LECTURE: FROM CLOSTRIDIUM WELCHII TO THE COXSACKIE VIRUSES: CHANGING MICROBIOLOGY. <i>Gilbert Dalldorf, M.D.</i>	396
ARTERIOSCLEROSIS AND DIABETES. <i>Ernst P. Boas, M.D.</i>	411
JUDICIUM DIFFICILE. A LESSON IN PERSPECTIVE. <i>Leo M. Davidoff, M.D.</i> ..	420
PERINEPHRIC AND RENAL CORTICAL ABSCESS DUE TO COLON BACILLUS WITHOUT BACTERIURIA OR PYURIA. <i>Kermit E. Ossermann, M.D., and H. Evans Leiter, M.D.</i>	424
SPONTANEOUS RUPTURE OF NORMAL GALL BLADDER DUE TO BILIARY TRACT OBSTRUCTION. <i>Alvin J. Kahn, M.D.</i>	428
ABSTRACTS.....	430

NUMBER 3, SEPTEMBER-OCTOBER, 1952

	PAGE
THE WILLIAM HENRY WELSH LECTURE. THE EARLY CHANGES CAUSED BY RADIATION. <i>Shields Warren, M.D.</i>	443
HISTOCHEMISTRY OF ENZYMES. <i>G. Gomori, M.D.</i>	446
RECENT OBSERVATIONS ON THE PATHOGENETIC MECHANISM OF IDIOPATHIC THROMBOCYTOPENIC PURPURA. <i>Mario Stefanini, M.D.</i>	452
TRANSMESENTERIC HERNIA. <i>Alfred A. Pomeranz, M.D. and Lester G. Step-pacher, M.D.</i>	465
SARCOIDOSIS WITH BRONCHIAL INVOLVEMENT. A REPORT OF TWO CASES WITH BRONCHOSCOPIC BIOPSIES. <i>Louis E. Siltzbach, M.D. and Max L. Som, M.D.</i>	473
THE JEWS' HOSPITAL AND PSYCHOLOGICAL MEDICINE. <i>Joseph Hirsh and M. Ralph Kaufman</i>	481
THE OSTEOHISTOLOGY OF THE NORMAL HUMAN VERTEBRA. ITS RELATION TO SCOLIOSIS AND CERTAIN LESIONS INCIDENT TO GROWTH AND SENES-CENCE. <i>Edgar M. Bick, M.D.</i>	490
ABSTRACTS.....	528
BOOK REVIEW.....	536

NUMBER 4, NOVEMBER–DECEMBER, 1952

	PAGE
A SUMMARY OF EXPERIMENTAL EVIDENCE RELATING LIFE STRESS TO DIABETES MELLITUS. <i>Lawrence E. Hinkle, Jr., M.D. and Stewart Wolf, M.D.</i>	537
PHYSIOLOGICAL CONSIDERATIONS OF EDEMA. <i>Marvin F. Levitt</i>	571
SOME THEORETICAL AND PRACTICAL ASPECTS OF THE USE OF FOLIC ACID ANTAGONISTS IN HUMAN NEOPLASIA. <i>Ezra M. Greenspan, M.D.</i>	583
TRIFACIAL (TRIGEMINAL) NEURALGIA WITH EMPHASIS ON ATYPICAL FORMS. <i>Ralph Howard Brodsky, D.M.D. and Norman A. Cranin, D.D.S.</i>	596
ELECTRON MICROSCOPY AS APPLIED TO CARDIOLOGY. <i>Bruno Kisch, M.D.</i> ...	606
ABSTRACTS.....	612

NUMBER 5, JANUARY–FEBRUARY, 1953

	PAGE
OBITUARY—JOSEPH H. GLOBUS.....	iv
RECENT ADVANCES IN THE THEORY OF THE MECHANISM OF BLOOD COAGULATION. <i>Mario Stefanini, M.D.</i>	619
EXPERIMENTAL APPROACHES TO PSYCHODYNAMIC PROBLEMS. <i>Jules H. Maserman, M.D.</i>	639
THE EXTRACELLULAR COMPARTMENT: A COMPARISON OF THE CHLORIDE AND INULIN SPACES. <i>Louis B. Turner, M.D. and Marvin F. Levitt, M.D.</i>	653
PERFORATION OF THE PYRIFORM SINUS. A SEQUELA OF ENDOTRACHEAL INTUBATION. <i>Milton H. Adelman, M.D.</i>	665
CORRELATION OF DENTAL ABNORMALITIES IN HYPO-PITUITARISM. <i>J. A. Salzmann, D.D.S. and Stanley L. Wein, D.M.D.</i>	668
MYOMA OF THE SECOND PORTION OF DUODENUM. CASE REPORT. <i>Alvin A. Bakst, M.D.</i>	677
EPILEPSY AND THE ELECTROENCEPHALOGRAM. <i>Louis Greenstein, M.D.</i>	683
ABSTRACTS.....	689

NUMBER 6, MARCH–APRIL, 1953

	PAGE
FOREWORD.....	iii
MEDICINE AND SOCIETY: AN HISTORICAL PERSPECTIVE. <i>Richard H. Shryock, Ph.D.</i>	699
MEDICINE AND SOCIETY: THE BIOLOGICAL FOUNDATIONS. <i>Paul Weiss, Ph.D., M.D. (Hon.)</i>	716
HEALTH, MEDICINE, AND ECONOMIC WELFARE. <i>Eli Ginzberg, Ph.D.</i>	734
MEDICINE AND THE COMMUNITY: THE ROLE OF THE VOLUNTARY HOSPITAL IN COMMUNITY MEDICAL CARE. <i>George Bachr, M.D.</i>	744
A CENTURY OF MILITARY MEDICINE. <i>Major General George E. Armstrong.</i> ...	754

	PAGE
PUBLIC HEALTH, 1852-1952. <i>Leonard A. Scheele, M.D.</i>	764
MEDICINE AND SOCIETY: THE ROLE OF PSYCHIATRY. <i>William C. Menninger,</i> <i>M.D.</i>	790
MEDICINE AND SOCIETY: IMPLICATIONS IN THE ATOMIC AGE. <i>Austin M.</i> <i>Brues, M.D.</i>	812
AN INTEGRATION. <i>Alan Gregg, M.D.</i>	821
INDEX TO VOLUME XIX.....	831

JOURNAL OF THE MOUNT SINAI HOSPITAL NEW YORK

VOLUME XIX • NUMBER 1

MAY-JUNE

ERNST P. PICK ANNIVERSARY VOLUME

CONTENTS

	PAGE
FOREWORD. <i>Joseph H. Globus, M.D.</i>	ix
ERNST PETER PICK, THE SCIENTIST. <i>Otto Loewi</i>	xii
TRIBUTE TO A LOST WORLD. <i>George Bachr, M.D.</i>	xiv
ON THE ACTION OF FLUORIDE ON THE HEART OF RANA PIPPIENS. PRELIMINARY NOTE. <i>O. Loewi</i>	1
SUSCEPTIBILITY TO CONVULSIONS IN RELATION TO AGE. <i>Alfred Frochlich, M.D.</i>	4
AMYLOIDOSIS IN MULTIPLE MYELOMA. PROGRESS NOTED IN 50 YEARS OF PERSONAL OBSERVATION. <i>A. Magnus-Levy, M.D.</i>	8
DIE WIRKUNG ELEKTRISCHER HYPOTHALAMUSREIZUNG AUF DEN EXPERIMENTELL ERZEUGTEN BRONCHIALMUSKELKRAMPF. <i>F. v. Brücke, F. Kaindl, H. Mayer, und A. Neumayr</i>	10
DISSEMINATED LUPUS ERYTHEMATOSUS. (MALIGNANT LUPUS ERYTHEMATOSUS (GOLDSMITH-BEAR)). SEINE GESCHICHTE—VERSUCH EINER BEGRIFFSBESTIMMUNG. <i>L. Arzt</i>	19
UEBER DIE NEUROGENE APPENDICOPATHIE. <i>H. Chiari</i>	30
ÜBER AUTOMATIK UND DEREN GRENZEN. <i>A. Durig</i>	38

GEWÖHNUNGSVERSUCHE AN FIBROBLASTENKULTUREN. <i>W. Heubner, M. Albrecht, E. Barocke, und H. Kewitz</i>	47
ANTIACCELERATOR CARDIAC AGENTS. <i>Otto Kraye, M.D.</i>	53
MODIFICATIONS OF THE HEART SOUNDS IN BUNDLE BRANCH BLOCK. <i>Stephen Contro, M.D. and Aldo A. Luisada, M.D.</i>	70
THE TRANSFER OF DRUGS INTO THE MILK. <i>Hans Mautner, M.D.</i>	83
EFFECT OF EXCESSIVE DOSES OF CORTISONE, ACTH AND PROLACTIN IN PREGNANT AND NURSING MICE. <i>Susi Glaubach, M.D.</i>	88
THE CHANGING PATTERN OF INFECTIOUS PROCESSES UNDER THE INFLUENCE OF CORTISONE. <i>William Antopol, M.D. and Howard Quittner, M.D.</i>	91
HUMAN AND EXPERIMENTAL ARTERIOSCLEROSIS. <i>David Lehr, M.D. and Jacob Churg, M.D.</i>	106
ZUR FRAGE DER ÜBERTRAGUNG SENSIBLER IMPULSE IN RÜCKENMARK DES FROSCHES. <i>Hans F. Häusler und Heinz Sterz</i>	121
INDICATIONS OF BED REST, PARTICULARLY IN THE AGED. <i>Albert Mueller-Deham, M.D.</i>	131
EXPERIMENTAL STUDIES ON RENAL CIRCULATION. <i>E. Rothlin and A. Cerletti</i>	138
THE EFFECT OF HISTAMINE ON AN ISOLATED SYMPATHETIC GANGLION. <i>H. Konzett</i>	149
ÜBER ANGRIFFSPUNKT UND WIRKUNGSWEISE MORPHINÄHNLICH WIRKENDER ANALGETIKA. <i>O. Schaumann</i>	154
"NICOTINIC ACTIVITY" AND THE PROBLEM OF PHARMACOLOGIC SELECTIVITY. <i>S. Locwe</i>	160
RESISTANCE TO GRAFTING WITH LYMPHOSARCOMA CELLS IN RATS INJECTED WITH HOMOLOGOUS LYMPHOID CELLS. <i>H. C. Stoeck, Tatiana Budziorovich, and T. C. Bielinski</i>	169
THE MODE OF ACTION OF ANTIBIOTICS: PENICILLIN AND STREPTOMYCIN. <i>W. W. Umbreit and E. L. Oginsky</i>	175
EINFLUSS DES DESOXYCORTICOSTERONS UND ANDERER STERINE AUF DIE ZELLMEMBRANDURCHLÄSSIGKEIT DER GELENKKAPSEL. <i>P. Stern</i>	185
DIE BEDEUTUNG DER EXPERIMENTELLEN PHARMAKOLOGIE FÜR DIE NEUROLOGIE UND PSYCHIATRIE. <i>Ottokar Arnold und Hans Hoff</i>	191
FIXATION OF COMPLEMENT WITH THE PURIFIED FACTOR IN MOUSE MILK CONNECTED WITH MAMMARY CARCINOMA. <i>Michael Heidelberger, Ph.D., Myron A. Leon, Samuel Graff, Ph.D., and C. D. Haagensen, M.D.</i>	210
ISOTOPICALLY LABELED NIRVANOL. <i>Harry Sabotka, Ph.D. and F. E. Stynler, Ph.D.</i>	212
EFFECT OF SOME REAGENTS ON THE FLUORESCENCE OF STILBAMIDINE AND 2 OH-HYDROXYSTILBAMIDINE IN VITRO. <i>F. Lieben, Ph.D.</i> ..	217
THE INFLUENCE OF EXPERIMENTAL HYDRONEPHROSIS AND OF SEVERAL AMINO ACIDS ON THE NEPHROTOXIC ACTION OF DL-ETHIONINE. <i>M. Wachstein and E. Meisel</i>	221
UPTAKE OF P ³² IN SEMINAL VESICLES OF CASTRATE RATS AFTER TREATMENT WITH TESTOSTERONE PROPIONATE. <i>Walter Fleischman, M.D., Ph.D. and Susan Kann Fleischmann, Ph.D. With the technical assistance of Ruth S. Raper, M.A. and Ida L. Gustus</i>	228

THE INTEGRATED ROLE OF CATECHOLAMINES, MINERALOCORTICIDS AND SODIUM IN HYPER- AND HYPOTENSION. (A WORKING HY- POTHESIS). <i>W. Raab, M.D.</i>	233
PHYSIOLOGIC AND PATHOLOGIC ALLERGY. <i>Bela Schick, M.D.</i>	240
THE RELATIONSHIP OF XANTHOMA JUVENILE TO SYSTEMIC RETICULO- ENDOTHELIOLOSIS. <i>Paul Freud, M.D.</i>	243
PROBLEMS IN JUVENILE DIABETES MELLITUS. <i>Richard Wagner, M.D.</i>	249
SERUM AND HEPATIC ENZYMES IN EXPERIMENTAL LIVER DAMAGE. <i>Hans Popper, M.D., Ph.D., Dieter Koch-Weser, M.D., and Jesus De La Huerga, M.D.</i>	256
BLOOD PRESSURES OF CHRONIC HYPERTENSIVE DOGS SURVIVING BI- LATERAL NEPHRECTOMY. <i>B. S. Oppenheimer, M.D., Stephen S. Rosenak, M.D., and Gordon D. Oppenheimer, M.D.</i>	266
ON THE INCIDENCE OF CARCINOMA IN CHRONIC ULCERATIVE COLITIS. <i>Sadao Otani, M.D. and Isidore Snapper, M.D.</i>	275
CORONARY ATHEROSCLEROSIS IN THE YOUNG: CLINICAL AND PATHO- LOGIC OBSERVATIONS. <i>David Adlersberg, M.D. and Frederick G. Zak, M.D.</i>	289
PROBLEMS IN THE MANAGEMENT OF REFRACTORY HEART FAILURE. <i>Charles K. Friedberg, M.D. and Mark Halpern, M.D.</i>	303
ACUTE GASTRIC DILATATION. <i>Ernest Gold, M.D.</i>	310
SOME OBSERVATIONS ON THE NUCLEIC ACIDS. <i>Samuel Graff, Ph.D.</i> ...	313
THE USE OF DIBENAMINE IN PHEOCHROMOCYTOMA AND DETECTION OF PRESSOR ACTIVITY OF THE PLASMA BY BIO-ASSAY. <i>Henry Haimovici, M.D.</i>	320
THE ECCRINOLOGICAL CLASSIFICATION OF GASTRIC MUCUS. <i>Franklin Hollander, Ph.D.</i>	328
THE INFLUENCE OF TOXIC AGENTS ON THE FEMALE GENITAL ORGANS. A BRIEF REVIEW. <i>Josef Novak, M.D.</i>	333
THE EFFECT OF THIOUREA ON MITOSIS IN RAT LIVERS DAMAGED BY CARBON TETRACHLORIDE. <i>M. Rachmilewitz and A. Rosin.</i>	339
LABORATORY AIDS IN THE DIAGNOSIS OF HYPERTHYROIDISM. <i>Solomon Silver and Sergei Feitelberg.</i>	345
PLUMBISM IN CHILDREN. <i>Frederick G. Zak, M.D. and William E. Finkelstein, M.D.</i>	352
ABSTRACTS	359
INDEX TO NUMBER 1, VOLUME NINETEEN	375

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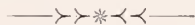
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TO
PROFESSOR ERNST PETER PICK

THIS SPECIAL ISSUE IS DEDICATED ON HIS
EIGHTIETH BIRTHDAY
BY HIS FRIENDS, ASSOCIATES AND PUPILS
IN RECOGNITION OF
HIS EXCELLENCY AS TEACHER AND SCIENTIST



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Mr. Joseph F. Cullman, Jr.	Dr. Eli Moschowitz	Dr. Lester Tuchman
Dr. Paul Freud	Dr. B. S. Oppenheimer	Dr. Max Wachstein
Dr. John H. Garlock	Dr. Samuel Peck	Dr. I. S. Wechsler
Dr. Leon Ginzburg	Dr. Abraham Penner	



Dr. Ernst P. Fickz

FOREWORD

The convulsive and disruptive events, which precipitately and tragically followed the advent of tyranny in Europe and its spread into Austria, brought Professor Ernst Peter Pick, who was still active as Professor of Pharmacology and Director of the Pharmacologic Institute of the University of Vienna, to the brink of disaster. It was then that his great virtues as man, scientist, and teacher saved him from a catastrophic fate.

All over the world, and particularly in the New World, there were many who recalled this truly modest, kind, unselfish man of great wisdom who had guided them in their first steps toward their scientific goal and was ever ready to help them in their efforts. They knew him as one who gave them generously not only of his time but also of his vast experience and of his treasured fruits of years of research, asking nothing in return. Their good will, their loyal devotion to the scientific spirit was all he ever sought, and he rarely took occasion, nor did he find cause, to be critical of lapses among his disciples.

These qualities stood him well always but more so at the time of urgent need when those who remembered his kindness and unselfish help—and of these there were many—promptly responded to his call and came to his rescue. It was the good fortune of the Mount Sinai contingent to be able to provide him with the opportunity to come to a free land and the home of those for whom he had kept open-door in his house of learning. A haven was provided where he would be safe from abuse, mental and physical, and where he would again be free to plan and work in his chosen field.

It was no easy task to begin anew in a strange environment, almost single-handed, and without the advantages he had enjoyed for so many years as head of a world-renowned department, where he was surrounded by countless aides and students. As the years advanced in nature's relentless way, and despite the turbulent state of the world's affairs, with waves of hope buffeting against waves of despair, there was no let up in the scientific efforts of Professor Pick. The results, their abundance and significance, are well reflected in the appended long list of work done and published by him since his arrival in the United States. They tell more than the spoken word of praise of the scientist and his accomplishments.

At the approach of his eightieth birthday, the pupils and colleagues of Professor Pick, eager to celebrate this event, thought it most appropriate for the occasion that an issue of the *Journal of The Mount Sinai Hospital* be dedicated to him as a token of esteem and gratitude. In this way his many old and newly acquired friends would join, either by contributing scientific articles or by sponsoring their publication, to pay tribute to one who is admired as teacher, investigator and, above all, as a most kindly man.

The Editorial Board of this *Journal* and the Administration of this *Hospital* welcomed the idea and with the completion of this most satisfying task are most pleased in the thought that they made possible a well deserved expression of high regard for the world-renowned man. They are aware of the happy coin-

cidence of celebrating the 100th year of the Hospital's service to the community and the 80th birthday of a most esteemed member of the Hospital Staff.

JOSEPH H. GLOBUS

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ERNST PETER PICK,
THE SCIENTIST

Enthusiastic scientific curiosity, striving for causal understanding, and strong persistency, which E. P. Pick displayed in his early years, permitted to anticipate that he would become an outstanding scientist. Fortunately enough he had the ability to select teachers and schools where he would find most favorable conditions for the development and later on for the realization of his potentialities. First he worked in biochemistry, especially that of proteins, under the inspiring leadership of the great Franz Hofmeister in Strasburg. It was the knowledge he acquired there, that may have suggested to him to turn to immunology. His ingeniously planned experiments, performed in Paltauf's laboratory in Vienna, proved to be fundamental for the successful development of the study of the specificity of proteins as antigens. The importance of this work was early recognized and that was the beginning of E. P. Pick's great reputation.

Nowadays strong specialization in science has become so common, that in most cases one is able to predict what the next publications will be about. In retrospect it appears that up to the twenties of this century this was very different. Usually one was looking forward anxiously to the changes of direction research of individual investigators would take. E. P. Pick fulfilled these expectations to a high degree. From immunology he turned to experimental pathology and later to pharmacology and made great contributions in so many different fields that it is impossible to enumerate them all. Nevertheless, one cannot refrain from enumerating a few of them, selected arbitrarily. Science owes to E. P. Pick most valuable studies and discoveries in the following fields: circulation especially of cold blooded animals, pharmacological action of single and combined hormones, thermo-, water-, and salt regulation, localization of the action of anesthetics in the central nervous system, conditions on which the effect of drugs depends, the mechanism of the "Lebersperre".

E. P. Pick was recognized as an originally minded scientist long before he joined H. H. Meyer, his great teacher in pharmacology and close friend. In succeeding him many years later, E. P. Pick became the heir of the most worthy tradition in pharmacology. This science had logically developed from physiology. In fact, Schmiedeberg, the father of pharmacology, was a student of the physiologist Carl Ludwig. Schmiedeberg recognized that drugs are exceedingly valuable tools for the study of organismic functions and that, on the other hand, knowledge of the mechanism of drug action would make for a better understanding of the therapeutical use of drugs. This physiological line of thoughts came as a heritage from Schmiedeberg to H. H. Meyer and from him to E. P. Pick. The importance of this direction in pharmacology was well recognized everywhere. This became evident by the fact that not only pharmacologists, but also physiologists and other experimental medical scientists from all over the world came to work with these leaders, as they had formerly come to Carl Ludwig. They were attracted by the prospect to learn, not so much special methods, as, in the main, the ways how to analyze observed phenomena by the attempt to probe into their very roots, and hereby to become acquainted with their meaning.

Anybody who had the privilege to work with E. P. Pick immediately felt the fine human atmosphere emanating from his kindhearted, helpful and extremely modest personality. It is a blessing that the versatility of mind which enabled him to fertilize so many fields and his eagerness to learn have remained with him to this very day. This has kept him abreast with the most recent developments in science and thereby he remained young and inspiring.

Ad multos annos.

OTTO LOEWI

TRIBUTE TO A LOST WORLD

GEORGE BAEHR, M.D.

On a late fall day in 1912, a very young American physician arrived in Vienna for a year of work and play in that delightful capital of Central Europe. Being so young and eager for new experiences, he spent his first days exploring the streets and byways of the city, strolling along the Ringstrasse, gazing into the fabulous shop windows on the Kärntnerstrasse, and drinking in the beauty and majesty of the Stefansdom. The streets and cafes were filled with happy, care-free people. The Hofoper and the theatres were crowded to the doors each evening, for this was the world's capital of music and the stage. Life was gay, for time was fleeting.

On his first Sunday in Vienna, the young physician wandered into one of the beautiful suburbs of the city, which later in the spring and summer he learned to love increasingly. Here happy families and young romantic couples enjoyed their weekly Ausflüge, tramping in stout shoes over the hills and through woods until they reached their favorite picnic ground or the shade of a famous inn. On these glorious days, they realized that life was to be lived— *Es lebe das Leben*. The mood of the people was joyous—soft and sweet. For it was still not quite two years before the dreadful cataclysm at Sarajevo that rocked the world.

The purpose of the young physician's presence in Vienna was his need to spend the better part of the next year in learning the techniques of experimental physiology as preparation for a future career in clinical research. So, on the following Monday, armed with an introduction from his former teacher, Professor Ludwig Aschoff of the University of Freiburg in Breisgau, at whose laboratory of pathology he had just spent a most profitable twelve months, the young man hurried from his modest pension in the Alsergasse to the famous Institute of Experimental Pharmacology for his early morning appointment with Professor Hans Horst Meyer, head of the Institute and professor of experimental pharmacology at the University. Arriving at the Institute before 8 o'clock, he learned his first Viennese lesson, that in prewar Vienna this ungodly hour was the middle of the night. He never hurried again while in Vienna and soon acquired the leisureliness of a true Viennese. Unfortunately, he lost the trait within 24 hours after returning to the hectic environment of his native land!

The first to arrive were the two dieners, Schneider and Kwapil, who constituted the entire non-professional staff of the Institute. They greeted the young physician most cordially, for two other Americans had left their mark at the Institute in previous years, George Whipple, who subsequently distinguished himself as professor of pathology and Dean of the Rochester Medical School and was awarded a Nobel prize for his contributions to the discovery of the cause and cure of pernicious anemia, and Henry Barbour, whose training at the Institute gained him the professorship of pharmacology at the Yale University School of Medicine.

As in most continental research laboratories of that day, the two dieners at the Institute did all the "seut" work, took care of the animals, assisted at animal experiments, helped prepare the demonstrations for student lectures, and performed an endless number of duties. In striking contrast to our modern American research centers, there were no other technicians. The young American soon



HANS HORST MEYER

learned that each scientific investigator, up to and including the director of the Institute, did his own laboratory work and performed his own experiments in detail. He could not, as in America, carry on his scientific investigations by remote control. For the young investigator, this constituted a valuable educational discipline.

The first member of the staff to arrive that morning, and almost every morning thereafter, was the Herr Geheimrat himself, for he was a Reichsdeutscher who had been called to the University from Marburg. In spite of the seductive influence of the Viennese environment, he was never able to cure himself of the incredible "tüchtigkeit" which characterized the typical German scientist. With all that, he was, nevertheless, one of the kindest and most considerate of men, admired by the entire University faculty and student body for his knowledge and integrity and loved dearly for his warm personality. He was of rather small stature, with a broad forehead, deep-set eyes, a sharp aquiline nose, finely chiselled features, and a small, careless beard. Although soft-spoken and gentle, he was nevertheless a man of firm character and belligerently loyal to his staff and his friends.

Addressing the American as "my young friend," he put the young man immediately at his ease by telling him that he had agreed with Aschoff's suggestion to accept him as a member of the Institute's family because the laboratory group at this time required someone who was trained in pathology and, more particularly, in experimental renal pathology. The only expense which the young investigator would be expected to meet would be the cost of his own experimental animals. In return for the privileges of the Institute, he would assist the professor and his staff in preparing the demonstrations required for student teaching and would collaborate with the first assistant of the Institute, Professor Ernst Peter Pick, in his experimental investigations.

It was characteristic of the old Geheimrat that he emphasized only one precept—that all the members of the staff were always to be of mutual assistance and to work together as a family. There was to be no secrecy about their scientific work. Each investigator was to be informed concerning his colleagues' research observations so that he could be helpful to them and could himself profit from the experience. The young American was deeply impressed by this spirit which permeated the Institute, where the motive was the unselfish promotion of scientific progress through group collaboration. It was an inspiring experience and a rare privilege which he has treasured for almost forty years.

On that first day, the Geheimrat's various assistants arrived between 10 and 10:30 o'clock and leisurely resumed their work at their laboratory work places, the animal operating room or the lecture hall. The first to arrive were usually the younger assistants, then either Professor Alfred Froehlich, whose name was associated with a pituitary syndrome, or the Erste Assistant, Professor Ernst Peter Pick. The young American was at first rather shocked by the late arrivals, but within a few days he was reassured by the observation that these men more than made up for the time loss by the fact that, once their work got under way, they seemed unable to tear themselves away from the laboratory until 1:30 or 2 p.m. Two hours for lunch was not exceptional. Although they seldom returned to the Institute before 3 or 3:30, the end of the afternoon found them again intensely engaged in their work and often unable to leave until 6:30 or 7 p.m.

At 6:30 most of the men repaired to the Cafe Karzer across the street where they foregathered for "Jause" around a "Stamitisch" with men from other re-

search laboratories of the University concerned with chemistry, physiology, pharmacology, and related disciplines. Here they spent a convivial hour or more, usually until about 8 o'clock, drinking coffee, exchanging experiences, reading various medical and scientific journals which were provided for their perusal by the Cafe, and discussing the newest problems of medical, biochemical, and physiological research. Scientific reputations were made or lost. For the young American, it was a most valuable educational experience. He learned to know members of the various medical school and university faculties in various parts of the world and to evaluate their scientific and clinical contributions. Lasting friendships were established and much helpful knowledge was acquired on a broad variety of subjects.

About 8 o'clock the last remnants of the group would break up and go off to their homes or their respective dinner engagements. After dinner the young American might visit the theatre, the opera, or a concert with his friends or he would spend an hour or two in the magnificent library of the Gesellschaft der Aerzte preparing for the next day's activities at the Institute.

On one evening a month, the assistants of the Institute foregathered in the home of the Herr Geheimrat for dinner—some after dinner. It was an informal company of six or eight, each of whom had been chosen by the Herr Geheimrat as his assistant because of specialized training and experience in a field which was not represented by the others. This typified the Herr Geheimrat's constant emphasis upon group collaboration in scientific research and teaching. The monthly gatherings in the home of the Herr Geheimrat also served to encourage a closer social integration between the various members of the team, but its primary purpose was that of a Journal Review Club. The young American was accepted into the warm circle of the laboratory family and, to his surprise, found himself treated as an equal. After almost four decades the monthly meets at the Professor's home remain vividly in his memory as one of the most delightful and profitable experiences of his life.

Judged by present-day standards of American research laboratories, the facilities of the Institute of Experimental Pharmacology were crude indeed. But the spirit as well as the competence of its small body of investigators more than compensated for the physical deficiencies. Professor Ernst Peter Pick was at that time the "Erste Assistant" and the leading personality upon whom the Herr Geheimrat placed most of the burdens of research direction. He was then in his 41st year. A former pupil of Hofmeister, he had come to the Institute from the field of biochemistry and was already known throughout the world for his contributions to the chemistry of proteins and their derivatives. His encyclopedic knowledge was at that time well exemplified by his volume on the Chemistry of Antigens published in the monumental work of Kolle-Wassermann.

It was the young American's good fortune to be assigned to work with him in a variety of physiological studies dealing with the physiological effects of altered cyclic and heterocyclic complexes of proteins. The half dozen or more publications which resulted during the next year and the knowledge and skills in experimental physiology which he acquired were far less important to him than the

influence upon him of Professor Pick's scientific and personal integrity, his habits of work and study, and above all his overwhelming kindness. He gave freely of his knowledge and time to everyone in Vienna who sought it. Almost daily, they streamed to his work desk from the clinical services and research laboratories of the University, seeking scientific information or guidance in their research program, usually without having appointments. He never was known to refuse his help to anyone. It annoyed the young American greatly to watch the daily proceedings, for it was obvious that the kind and generous Professor was allowing all Vienna to "pick his brains" at the sacrifice of his own research work. To compensate in part for these interruptions, he was frequently obliged to continue at his work desk until well into the evening so as to complete an experiment or a technical procedure which could not be left for the next day. If it had not been for some of his devoted laboratory colleagues and friends, who literally dragged him from his work, he would often have missed his "Jause," an absolute "must" for every Viennese at the end of the day.

This happy time ended for the young American late in the summer of 1913 when he reluctantly parted from his Viennese friends and returned to America. Within a year, the world as they knew it came to an end. However, he was to see them once again during the war years, quite unexpectedly. In 1915, poverty, suffering, and filth brought on by war resulted in a raging epidemic of typhus fever among the population of the Balkans which threatened to spread through Europe like the Black Plague. The young American found himself in Serbia as a member of an American sanitary commission financed by the American Red Cross and headed by the late Dr. Richard Pearce of Harvard. In September and October of that year the armies of the Central Powers rolled down over the Balkans and the young American, although a member of a still neutral nation, was taken prisoner by the Bulgars. It was then that the good Viennese revealed their full capacity for friendship.

Someone in Vienna noticed the young American's name in the list of captured in the Austro-Hungarian War Office and gave the information to his friends at the Institute. They promptly determined to rescue their young American friend from the hands of their Bulgarian allies, in whose mercy they had small confidence. Two other members of the faculty of the University, Professors Wenkebach and Paltauf, were persuaded to join with Professor Meyer in an appeal to the Austro-Hungarian War Office to secure the American's release from the Bulgars on the pretext that, as a member of a neutral country, he might collaborate in a study of a similar epidemic of typhus fever that was raging at that time on the Russian front. It was during the course of this special mission that the young American again spent several weeks in Vienna in 1916 on his way to and from the Russian front and was able to thank them for their intercession.

By that time Vienna had already changed. Laughter and gaiety had been replaced by a general feeling of deep discouragement. Professor Meyer and Professor Pick were in despair. But it was Professor Landsteiner whose profound depression, based upon a conviction that the world as he knew it was coming to an end, affected all who had contact with him.

This brings the brief sketch of the pre-war experiences of a young American physician in Vienna to a close except for one more incident. Although intended to portray a little of the life and times of the Vienna in which Professor Pick lived and worked almost forty years ago, this story could not avoid devoting attention also to Professor Meyer, for the two were inseparable. The relationship was like that of a father and a devoted son. In fact, such a relationship actually developed when Professor Pick married the Herr Geheimrat's daughter.

Mention has already been made of the loyalty of Professor Meyer to his pupils and friends. This was best revealed by his actions some years before World War I when the predecessor of Professor Pick as Dr. Meyer's first assistant was Professor Otto Loewi. When the faculty of the University of Graz selected Loewi *primo loco* for the chair in experimental pharmacology, the anti-Semitic student body, already fascistically inclined, rebelled violently against the appointment and threatened the Austrian Ministry of Education if the appointment was confirmed. Without a moment's hesitation, Professor Meyer proceeded to the Ministry and tendered his resignation from the Viennese faculty to take effect immediately if the Ministry should accede to the demands of the anti-Semitic students at Graz. Professor Loewi's appointment was confirmed. Soon thereafter his faculty membership lent great luster to this University when he was selected as the recipient of the Nobel prize in medicine.

Upon Professor Meyer's retirement from the chair in experimental pharmacology at the University of Vienna, the logical successor was his first assistant, Ernst Peter Pick. By that time the Nazis in Germany and Austria were already beginning to spread their malicious political and racial propaganda, although they had not yet come to power. In spite of Professor Pick's scientific reputation throughout the world, it is doubtful whether his appointment as Meyer's successor would have been possible at that time if it had not been for the memory of the former incident at Graz.

Today, America is proud of its role as the haven of refuge for these remarkable Viennese scientists. After 1923 Landsteiner spent the remainder of his life at the Rockefeller Institute; Loewi is still actively engaged in research at New York University School of Medicine and in summer at Woods Hole. But we are especially proud that our own beloved Ernst Peter Pick is with us at the Mount Sinai Hospital where he can continue to be an inspiration and guide to the present generation as he was for that young American who sat at his feet in the Vienna of long ago.

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ON THE ACTION OF FLUORIDE ON THE HEART OF RANA PIPIENS*†

PRELIMINARY NOTE

O. LOEWI

In continuation of earlier studies on the action of pressor and depressor agents on the frog's heart (1) I investigated the influence of fluoride and found that small doses cause an increase of the amplitude. For various reasons it seemed worthwhile to find an explanation of this unexpected effect.

EXPERIMENTS

Addition of NaF (final concentration M/400 to M/200) to a non-optimally beating heart produces a gradual increase of the amplitude of the beat. The effect starts within two to four minutes, reaches its maximum in about 10 to 20 minutes, and lasts almost indefinitely. In order to remove the fluoride, when the maximum amplitude has been reached, the heart has to be washed out repeatedly. Even so the heart returns to the initial level only after considerable time has elapsed. The difficulty in removing the NaF by washing out demonstrates that NaF is fairly strongly fixed on the heart.

It was found that the addition of NaF also increases the amplitudes of hearts perfused with Ringer with diminished Ca content. The degree of the effect depends on the degree of the Ca diminution. After reduction of Ca to one half or even one quarter, NaF often increases the amplitude to the level previously maintained in normal Ringer.

NaF furthermore restores, often completely, the activity of hearts depressed by an excess of K in the perfusate. It regularly causes complete recovery of hearts made hypodynamic by long continued perfusion with Ringer (2). The hypodynamic state in this case results from the effect of the K in the Ringer which predominates over the calcium effect.

The effect of NaF is not restricted to cases where the depression is caused by K. It also increases the heart beats previously depressed by decreasing the Ca content of K-free Ringer. Finally it restores the heart from depression by such agents as magnesium chloride or sodium citrate.

The question now arises as to the mechanism by which NaF exerts the above effects. A clue to the solution of this question might be given by considering the effects of certain lipoids which are normal constituents of the heart cell and play a part in its physiological function. Clark (2) showed, many years ago, that the hypodynamic state of the heart which, as mentioned before, develops after long time of perfusion with Ringer, is caused by the loss of lipoids. He could, in fact, demonstrate that their addition to the Ringer immediately restored the heart.

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The lipoids could be substituted by soaps such as sodium oleate which form difficultly soluble Ca salts. Later it was found that addition of oleate also increased the resistance of the fresh heart to the depressant influence of excessive K (1) diminished Ca, and other agents (3). The effects of NaF and oleate thus appear to be very similar. The same final effect of drugs may of course result from quite different mechanisms of action. We have therefore to check whether NaF and Na oleate share properties which would justify the contention that the effects of NaF are due to a fundamental mechanism similar to the one ascribed to oleate. Both are strongly attached to or combined with cell constituents as evidenced by the difficulty of removing them from the heart by washing out. The affinity of oleate may at least partly be due to its strong surface activity. As to the character of the cell constituents to which they are fixed, we only know that NaF combines with magnesium and other metals; we do not know whether just these combinations are responsible for the effects we are here concerned with.

Furthermore, both NaF and oleate also combine with the cells in the absence of Ca in the perfusate as becomes evident from the following result: they were added to Ca-free Ringer in the heart and left there for a while. Then this Ringer was removed and replaced by Ringer with reduced Ca or increased K content. Immediately the amplitude of the beats rose to the same height as it did when NaF or oleate had been added to Ca containing Ringer.

Finally, NaF and oleate have in common that they form sparingly soluble Ca salts. This tends to show that not only their final effects are similar, but that they also share properties which could be responsible for their effects. We have therefore to deal with the question as to how these effects could come about.

Such antagonistic effects against depressant factors as were reported, can also though only within certain limits, be produced by increasing the concentration of Ca in the perfusate. Therefore, one might be inclined to assume that the effect of NaF and oleate would consist in sensitization of the heart to the effect of Ca. So far sensitization to Ca has been observed only in cases of long lasting Ca deficiency produced by perfusion with Ca and K-free Ringer and with digitalis. The state of Ca sensitization in these cases is characterized by diminished diastolic relaxation. This symptom, also produced by excess of Ca, has however never, not even transitorily, been observed during NaF or oleate action. On the contrary, in all cases of recovery by NaF or oleate the diastolic relaxation as well as the systolic contraction were increased. This fact would suffice to reject the assumption that these agents might act by sensitization of the heart to the effect of Ca.

We therefore have to look for another explanation of the mode of action of NaF and oleate. It has been known for decades, especially from studies on monocellular and other lower organisms, that Ca is needed not only for certain specific functions. It also is needed for the preservation of the normal physico-chemical state of the cells on which depends such behavior as their ability to resist all kinds of damage. There exists to my knowledge no definite evidence of whether or not Ca is able to fulfill this general cell function as free ionized Ca.

At least in Clark's aforementioned experiments the perfused heart in spite of the presence of a normal concentration of Ca in the perfusate, lost its resistance to the action of K simultaneously with the loss of lipoids and regained it only after addition of lipoid or oleate. Clark (4) already suggested that "the action of the lipoids might be due to some alteration in the condition of the calcium which causes its fixation on the heart surfaces." It would suggest itself that this alteration consists in the formation of the difficultly soluble Ca oleate and that this is fixed on the heart. The same may be true for Ca fixation by means of fluoride, as this agent which restores the heart from the hypodynamic state exactly as does oleate, also combines with heart constituents and also forms a difficultly soluble Ca salt.

After all the hypothesis seems to be well supported that fixation of Ca on the heart by means of NaF as well as of oleate might be one of the factors responsible for an optimal physicochemical state of the heart and hereby for its resistance against depressants. This hypothesis would obviously explain the effects of NaF we observed.

SUMMARY

1. Small doses of sodium fluoride increase the amplitude of the beats of the isolated heart of rana pipiens.
2. The same doses are effective when the amplitude is decreased by depressant drugs or conditions as: excess of potassium, diminution of calcium, and the hypodynamic state produced by continuous perfusion.
3. The similarity of the effects of sodium fluoride and sodium oleate as well as a hypothesis on the underlying mechanism of these effects is discussed.

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SUSCEPTIBILITY TO CONVULSIONS IN RELATION TO AGE*

ALFRED FROEHLICH, M.D.

This report describes studies on the relation of age to susceptibility to convulsions in animals. The purpose of the investigation has been to shed light on the mechanisms involved in the increased susceptibility of infants and young children to convulsive disorders.

Since the rat has been found to be an excellent experimental animal for pharmacological studies on convulsions (1, 2) this species was chosen to observe the effect of various convulsant drugs at different age levels.

In 1942, in conjunction with I. A. Mirsky, the effect of acid fuchsin** on the production of convulsions in albino rats of various age levels was reported (3). In this study, the acid fuchsin was subcutaneously administered in a 2 to 5 per cent solution in a dose of from 0.5 to 2.0 mg. per gm. of body weight. 395 rats, divided into groups of 10 to 40 days by age, were observed following the injection of this water soluble sulfonated dye. The youngest group of rats chosen were 7 days of age, and a separate group for each succeeding day of age up to 25 days were studied. Rats over 100 days of age were grouped together and considered as adults. When convulsions were noted, they occurred within four hours, lasted several hours, and in the majority of instances, proved fatal. The results of this experiment were quite striking. Up to and including the age of 17 days, 75 to 100 per cent of the animals responded to the dose of 0.5 mg./gm of body weight with convulsions. On the eighteenth day of life, the incidence of convulsions following the administration of the acid fuchsin dropped precipitously reaching zero on the twentieth day. After that age, the 0.5 mg. dose was ineffective as a convulsant. Raising the dose of acid fuchsin to 1.0 mg. per gram of body weight was found to produce an entirely similar pattern except that the appearance of convulsions in a significant percentage of animals was extended to 22 days of age. With the highest doses employed (2.0 mg./gm. body weight), 30 per cent of the 25-day old animals still responded with convulsions but these were noted in only 7 per cent of 44 adult animals. In these, intracerebral injection of 0.1-0.5 mg. of acid fuchsin always resulted in the prompt development of severe convulsions.

In another experiment the influence of bile on the susceptibility to convulsions in relation to age was investigated (4). Groups of rats of both sexes, ranging in age from 1 to over 100 days were tested with various doses of bile.† The bile was administered intraperitoneally in a 1% solution and the dosage varied from 0.1 to 1 mg. of bile per gram of body weight. When convulsions appeared, they were noted within 100 minutes, lasted several hours, and in a few instances terminated fatally.

The results of these experiments are shown in Table I.

* From The May Institute for Medical Research of the Jewish Hospital Association, Cincinnati, Ohio.

** The acid fuchsin employed was purchased from Coleman & Bell Co., Norwood, Ohio.

† Parke Davis and Company "Concentrated Bile."

From the data in Table I, it will be noted that the intraperitoneal injection of bile results in the production of convulsive seizures in rats up to 10 days of age and not thereafter. However, when 1 mg. of bile in a 1% solution was introduced directly into the brain of adult rats, by way of a trephine opening, clonic convulsions began within 10 minutes. That the bile did not penetrate the older animals brain, but probably did in the less than 10 day-old rats, is suggested by the histological studies. Examination of the brains of adult animals after the intraperitoneal injection of bile revealed no pigment, whereas within two hours of the injection, the brains of bile-treated young animals (up to 10 days) occasionally revealed the presence of pigment in various parts of the brain. This is consistent with the observations of Orth (5) who in 1875 pointed out that the brains of young children dying with jaundice may be icteric, while those of severely jaundiced adults are not.

Since acid fuchsin belongs to the class of neutrophilic dyes which do not stain the nerve cells of the brain of the adult animals but do stain those of the young animals (6), it may be speculated that since convulsions are produced in the young animal and not in the adult, some mechanism related to the passage of

TABLE I

Susceptibility to Convulsions in Different Age Groups after Administration of Bile

AGE (DAYS)	NO. OF ANIMALS	DOSE (MG./GM.)	NO. WITH CONVULSIONS	% WITH CONVULSIONS	% DEAD
1-5	37	0.1-0.5	34	92	12
6-10	16	0.1-0.5	13	81	6
11-15	11	0.3-1.0	0	0	0
16-adult	22	0.5-1.0	0	0	0

the dye into the brain tissue is associated with the susceptibility to convulsions. The findings noted after the intraperitoneal injection of bile are entirely consistent with this hypothesis and suggest the development of some ill-defined "hematoencephalic" or "blood-brain barrier" in adults which limits or prevents the transfer of certain agents from the vascular tree into the nerve tissue. The development of a hematoencephalic barrier in the adult animal has been speculated on by several others who have presented experimental data which are consistent with such a viewpoint (7, 8).

The functional nature of this "barrier" is supported by our studies with theophylline. Theophylline increases the permeability of isolated blood vessels (9), and increases the ability of many tissues to take up various dyes (10). In earlier studies with Zak (11, 12) we had pointed out that theophylline will allow ferrocyanide to penetrate guinea pig brains, a phenomenon which did not occur in untreated animals; and that theophylline in frogs will decrease the latent period observed before the onset of convulsions consequent to the injection of acid fuchsin.

When adult rats were given two subcutaneous injections of from 0.12 to 0.24 mg. of theophylline with sodium acetate per gm of body weight at four hour

intervals, they were made readily susceptible to the convulsant action of subcutaneously administered fuchsin (3). The doses of acid fuchsin employed were incapable of producing convulsions in non-theophyllinized adult rats. The effects were even more striking when the acid fuchsin was injected intraperitoneally. Here, doses of 0.25 mg./gram of body weight were effective in producing convulsions in the theophyllinized adult rats, whereas 8 times the dose of acid fuchsin administered by the same route was ineffective as a convulsant in non-theophyllinized animals of the same age. More recently attempts have been made to decrease the effectiveness of convulsant doses of acid fuchsin in young rats. To date, most success in this respect has been achieved with large doses of Vitamin D.* The dose of vitamin employed, 500 to 1500 units per os daily beginning at 4 to 5 days of age, produces evidence of hypervitaminosis. This is manifested by retardation of growth, the appearance of baldness, and degenerative changes in the skin. The latter changes are extremely interesting and will be the subject of a separate communication.

TABLE II
The Effect of Hypervitaminosis D on the Susceptibility of Young Rats to the Convulsant Action of Acid Fuchsin

NO. OF ANIMALS	AGE (DAYS)	AGE AT ONSET OF VITAMIN D THERAPY	VITAMIN D RECEIVED TOTAL (UNITS)	DOSE ACID FUCHSIN (MG./GM. BODY WT.)	NO. WITH CONVULSIONS	NUMBER DEAD
3	14	6	8,000	0.5	1*	0
3	15	6	8,000	0.5	0	0
2	14	Control	0	0.5	2	2
1	15	Control	0	0.5	1	1

* Convulsion described as slight and very transient.

The Vitamin D treated animals proved much more resistant to the convulsant action of subcutaneously administered acid fuchsin than normal controls. A typical experiment, representing one of many, is described in Table II.

From the data, the characteristic response of young animals to acid fuchsin after previous treatment with Vitamin D can be seen to be quite different than the controls. In only one of the experimental animals was a convulsion noted, and that was a minor one. In all the control animals fatal convulsions promptly occurred.

Similarly, it was found that Vitamin D could protect against the convulsant action of bile in young rats. Finally, we have been able to demonstrate that the protective action of hypervitaminosis D in young rats can be negated by the administration of theophylline prior to the injection of acid fuchsin.

The studies reported in this communication can be summarized as follows:

1. Acid fuchsin subcutaneously administered to rats acts as a convulsant in young animals but is ineffective in the adult rat. The intracerebral injection of acid fuchsin produces convulsions in adult rats.

* Viosterol was employed as a source of Vitamin D (Irradiated Ergosterol).

2. The intraperitoneal injection of bile results in the production of convulsive seizures in rats up to 10 days of age and not thereafter. The intracerebral injection of bile produces convulsions in adult rats. Bile pigment is capable of permeating the nervous tissue from the vascular system in young rats, but not in adult rats.

3. The administration of theophylline to adult rats renders them susceptible to the convulsant action of acid fuchsin.

4. Hypervitaminosis D decreases the susceptibility of young rats to the convulsant action of acid fuchsin and bile.

5. Theophylline can restore to normal the impaired susceptibility of hypervitaminotic D rats to the convulsant action of acid fuchsin.

6. These findings are consistent with the hypothesis of the development of a functional type of "hematoencephalic barrier" in older animals which controls the transfer of some agents from blood to brain. This "barrier" can be altered by theophylline and Vitamin D.

7. One of the factors responsible for the increased liability of young children and infants to convulsive disorders may be the lack of development of such a "barrier."

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AMYLOIDOSIS IN MULTIPLE MYELOMA

PROGRESS NOTED IN 50 YEARS OF PERSONAL OBSERVATION

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Amyloid was discovered about a century ago by Virchow. Its enormous accumulation in the liver and spleen, in neglected cases of tuberculosis and hues—the like nowadays are met with but rarely—aroused intense attention. Pathologists then were faced with two major problems: with the nature of this strange metabolite and its site of origin. Answers to these questions at that time were purely speculative. Even if somebody by mere chance had been on the right track, means were not available for attacking the problem. In the above diseases amyloid apparently is a secondary problem.

In the second half of the 19th Century, knowledge was won of a new disease, now known as multiple myeloma, in which amyloid seems to be a primary product of deranged metabolism. Its outstanding symptom was hit upon by Bence Jones in 1848, almost at the same time as Virchow discovered amyloid. A patient of Bence Jones excreted no less than 60 grams of a strange protein, widely different from all then known. Justly, now it bears his name. Since amounts of 30 to 77 Gm. a day have been reported 14 times, that derangement of protein metabolism is not inferior to that of the carbohydrates in diabetes. Quite a long time after Bence Jones' publication his protein proved to be frequently associated with a second anomalous product, the hoarding of huge amounts of amyloid. Since its accumulation differed somewhat from the classical deposits it was called by some authors "paramyloidosis." Though the first reports date as far back as 1875 and 1893, their number grew rather slowly at first, then more rapidly when in the twentieth century they were carefully searched for. Up to 1893 I was able to tabulate no less than 38 cases from 150 reports of multiple myeloma. In fact, as to its relative frequency, Bence Jones disease surpasses by far all other diseases.

From my very first lecture in 1931 (1), I laid stress upon the concomitant occurrence of amyloid and the Bence Jones protein for better understanding of both of them.

About the origin of the latter from the myeloma cells, there scarcely ever has been any doubt in the mind of experts. In 1938, I strongly advocated that amyloid must be produced by those very same cells. Heavy amounts thereof were found within intraosseal tumors, and when their cells had been squeezed to death by the growing pressure and vanished, the intervertebral gaps were filled by amyloid substance. This could be understood only if it had been produced by the myeloma cells (2).

Recently, in 1950, this assertion was confirmed to be true or rather proved directly through a very fine piece of work by Herbut and Erf (3) and verified by Bayrd and Bennet. They examined myeloma cells, not post mortem, but

taken from the sternum of the patient through marrow aspiration. These cells, being fresh and not overaged, contained amyloid. "Since the plasma cell is not phagocytic, this should be rather conclusive evidence of the site of origin." It is!

In the meantime the question may be raised wherefrom does the amyloid stem in the classical amyloidosis in the absence of tumorous cells. The answer will be, they originate in the normal plasma cells. Under the impact of chronic infects and other stimuli, they certainly will be able to produce amyloid, though more slowly and on a minor scale. There is no definite, no absolute boundary between physiological and pathological metabolism.

One problem of amyloid formation thus having been solved, the other, as to its nature, remains to be settled. It will be settled when amyloid will be isolated in a fairly pure substance. I am confident that this will be possible, and I am confident also that a relationship to other proteins then will be established. It remains to be seen whether this will show up in the direction of the soluble small Bence Jones proteins (Mol. w. 36000) or of the viscous larger ones of the "euglobulin family" (Mol. w. 108000), and what the relationship may be with the euglobulins and other abnormal proteins.

With interest continued and present day technique improved the time for final solution may not be too far off.

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DIE WIRKUNG ELEKTRISCHER HYPOTHALAMUSREIZUNG AUF DEN EXPERIMENTELL ERZEUGTEN BRONCHIALMUSKELKRAMPF*

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In einer Reihe von Veröffentlichungen haben wir uns mit Unterschieden beschäftigt, die zwischen einer direkten elektrischen Reizung hypothalamischer sympathischer Zentren und der reflektorisch durch Drucksenkung im Carotissinus ausgelösten Sympathieerregung bestehen.

Wir (1) fanden bei Katzen in Chloralosenarkose in Übereinstimmung mit Ergebnissen von Houssay und Molinelli (2), dass bei elektrischer Reizung des Hypothalamus eine erhebliche Steigerung der Inkretabgabe aus dem Nebennierenmark stattfindet. Während in Kontrollperioden dieses Inkret zu 6–20% Adrenalin und den Rest Noradrenalin enthält, wird bei Hypothalamusreizung 40–80% Adrenalin gefunden. Demgegenüber wird beim Abklemmen beider Carotiden an vagotomierten Katzen die Inkretmenge wesentlich weniger vermehrt (3). Kaindl und v. Euler (4) haben kürzlich beschrieben, dass es hierbei auch nicht zu einer Verschiebung im relativen Gehalt an Adrenalin und Noradrenalin kommt.

Es war zu erwarten, dass die erhöhte Adrenalinabgabe an das Blut sich auch an den peripheren Erfolgsorganen bemerkbar machen musste. Tatsächlich fanden Brücke, Loudon und Werner (5) an isoliert durchströmten Hundeextremitäten während der Hypothalamusreizung Wirkungen wie nach intravenöser Injektion von Adrenalin. Sowohl an normal innervierten, als auch an denervierten Beinen tritt bei Hypothalamusreizung, wie bei Adrenalininjektion zunächst symmetrisch eine Steigerung der Durchblutung auf (Erweiterung der Muskelgefäße), die später einer Verminderung durch Vasokonstriktion weicht. Dagegen wird bei Drucksenkung im Carotissinus bei gleicher allgemeiner Blutdrucksteigerung auf der innervierten Seite sofort Vasokonstriktion beobachtet, während die denervierte Seite druckpassiv vorübergehend mehr durchblutet wird. Die Reaktion ist also in diesem zweiten Fall unsymmetrisch.

Es schien uns wichtig, auch an einem anderen Versuchsobjekt, nämlich der Weite des Bronchialbaumes, die Wirkung der beiden Erregungstypen des Sympathikus zu untersuchen. Bisher wurde wohl bei Drucksteigerung im Carotissinus von Houssay und Orias (6) sowie neuerdings von De Burgh Daly und Schweitzer (7). Bronchokonstriktion gesehen, doch hatte die Drucksenkung keine bronchialerweiternde Wirkung. Bei elektrischer Reizung des Sinusnerven haben die genannten Autoren sowohl verengende, wie auch erweiternde Wirkungen am Bronchus gesehen. De Burgh Daly und Schweitzer glauben, dass die erweiternden Wirkungen den afferenten Chemorezeptorenfasern zuzuschreiben sind.

Experimente mit direktem Nachweis einer Wirkung der Hypothalamusreizung auf die Bronchialmuskulatur scheinen nicht vorzuliegen, wenn auch Hess (8) an eine derartige Möglichkeit denkt.

* Aus dem pharmakologischen Institut der Universität Wien. Vorstand: Prof. F. v. Brücke.

METHODIK

Zu unseren Versuchen verwendeten wir 11 Hunde beiderlei Geschlechts im Gewicht von 7–17 kg, wobei wir ältere Tiere bevorzugten. Die Tiere erhielten eine Stunde vor dem Versuch 5 mg/kg Morphin i.m. und wurden mit 0,07 g/kg Chloralose i.v. narkotisiert. Die Registrierung des durch Pilokarpin i.v. erzeugten Bronchospasmus erfolgte nach der von Konzett und Rössler (9) ausgearbeiteten Methode. Hierbei wird bei eröffnetem Thorax die Lunge mit der Starlingpumpe mit einem konstanten Luftvolumen bei gleichbleibendem positivem Druck beatmet.

Dieser Druck wird dadurch erzeugt, dass ein Nebenarm der Trachealkanüle über ein Rohrsystem unter Wasser ausmündet. Bei Verengung des Bronchialbaumes wird nicht mehr das gesamte Luftvolumen von der Lunge aufgenommen, sondern strömt zum Teil durch dieses Rohr aus und wird mit einem "Pistonrekorder" fortlaufend registriert. Es ist dafür gesorgt, dass sich der "Pistonrekorder" bei jeder Expiration vollkommen entleert. Zur Erhöhung des Bronchialtonus wurde von 2–60 mg Pilokarpin i.v. gegeben. Trotz hoher Dosen konnte in 3 Versuchen kein Bronchospasmus erzielt werden. Da unter Pilokarpin Herzstillstand eintreten kann, muss das Herz nötigenfalls vom Herzohr aus durch elektrische Reize künstlich getrieben werden.

Beide Nn. vagi und beide Carotiden wurden am Hals freigelegt und in 6 Versuchen wurde auch der N. splanchnicus auf beiden Seiten dicht oberhalb des Zwerchfells ange-sehungen.

Die elektrische Hypothalamusreizung erfolgte nach Trepanation des Schädels über dem tuber parietale durch eingestochene, bis auf die Spitze isolierte Elektroden aus V₂A-Stahl-draht (0,4 mm einschliesslich der Isolation). Die Elektroden hatten einen Abstand von 2 mm und wurden in die mittlere Hypothalamusgegend dicht über dem tuber cinereum eingestochen (Kontrolle am formolgehärteten Gehirn). Zur Reizung verwendeten wir exponen-tiell an- und absteigende Stromstösse (200 Hz) Stromstärke maximal 2,5 Mamp. Bei starken Stromstärken trat manchmal Muskelzittern auf. Der Blutdruck wurde aus der art. femoralis mit einem Hg-manometer geschrieben.

ERGEBNISSE

Das Abklemmen beider Carotiden (Drucksenkung im Carotissinus) führte in keinem Versuch zu einer Lösung des Pilokarpinkrampfes, auch dann nicht, wenn beide Nn. vagi durchschnitten waren. Die Blutdrucksteigerung konnte dabei bis zu 60 mm Hg betragen. (Abb. 1).

Dagegen trat nach elektrischer Hypothalamusreizung regelmässig nach einer Latenz von mehreren Sekunden Broncholyse ein die durch Veränderung der Stromstärke variiert werden konnte. Gleichzeitig stieg der arterielle Druck in der arteria femoralis steil an. Nach Beendigung des Reizes stellte sich mit der Rückkehr des Blutdruckes zur Norm der Bronchialmuskelkrampf wieder ein. Dies trat auch dann ein, wenn die Blutdrucksteigerung im Vergleich zu der nach Carotidenabklemmung unbeträchtlich war.

Um eine annähernd gleichstarke Erschlaffung der Bronchien zu erzielen benötigten wir intravenöse Adrenalingaben von 3–20 µg. Wir verwendeten stets mit Ascorbinsäure stabilisierte 1-Adrenalinhydrochlorid-lösungen.

Es scheint jedoch, dass bei intaktem Halsvagus der Effekt am Blutdruck und an der Bronchialmuskulatur etwas geringer ausgeprägt ist. Die Ausschaltung der Nn. vagi bewirkt die Lösung des Bronchialmuskelkrampfes jeweils für längere Zeit, sodass zur Erzielung eines neuen Bronchospasmus Pilokarpin nachinjiziert werden muss.

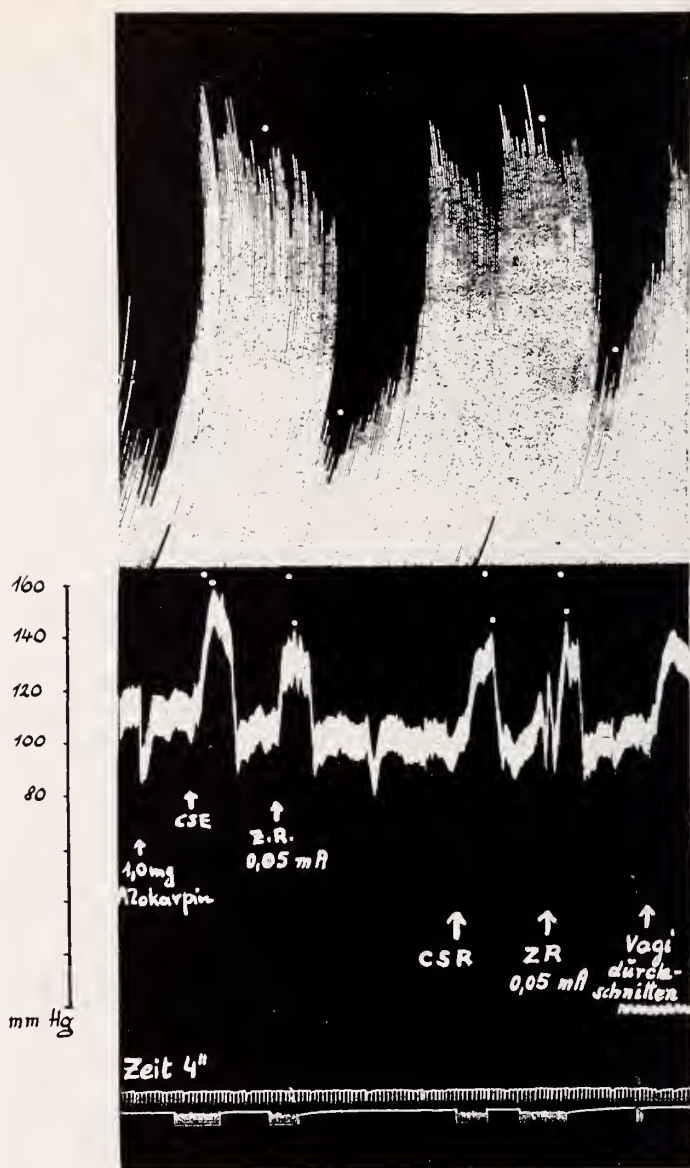


ABB. 1. Weibl. Hund 16kg. Narkose: 0,005mg Mo./kg, 0,07g Chloralose/kg. 1,0g Pilokarpin i.v. Oberste Kurve: Bronchialregistrierung siehe Text. Mittlere Kurve: Blutdruck. Zeit 4sec. Weiße Punkte: Synchronmarken. Nn.vagi intakt. Bei Pfeil 1.) 1mg Pilokarpin i.v. 2.) Abklemmen beider Carotiden (CSE) 3.) Elektrische Hypothalamusreizung (0,05mamp) 4.) CSE 5.) Hypothalamusreizung mit 0,05mamp.

In einem Versuch wurden beide Nebennieren des Tieres umfassend ligiert, trotzdem konnten wir bei Hypothalamus-Reizung bei Anwendung der 4fachen Stromstärke gegenüber vorher noch volle Bronchialerschaffung erzielen. Auch beiderseitige Splanchnikusdurchschneidung unmittelbar oberhalb des Zwerch-

felles hob in anderen Versuchen die broncholytische Wirkung der Hypothalamusreizung nicht auf, auch hierbei musste jedoch die Reizstärke vergrößert

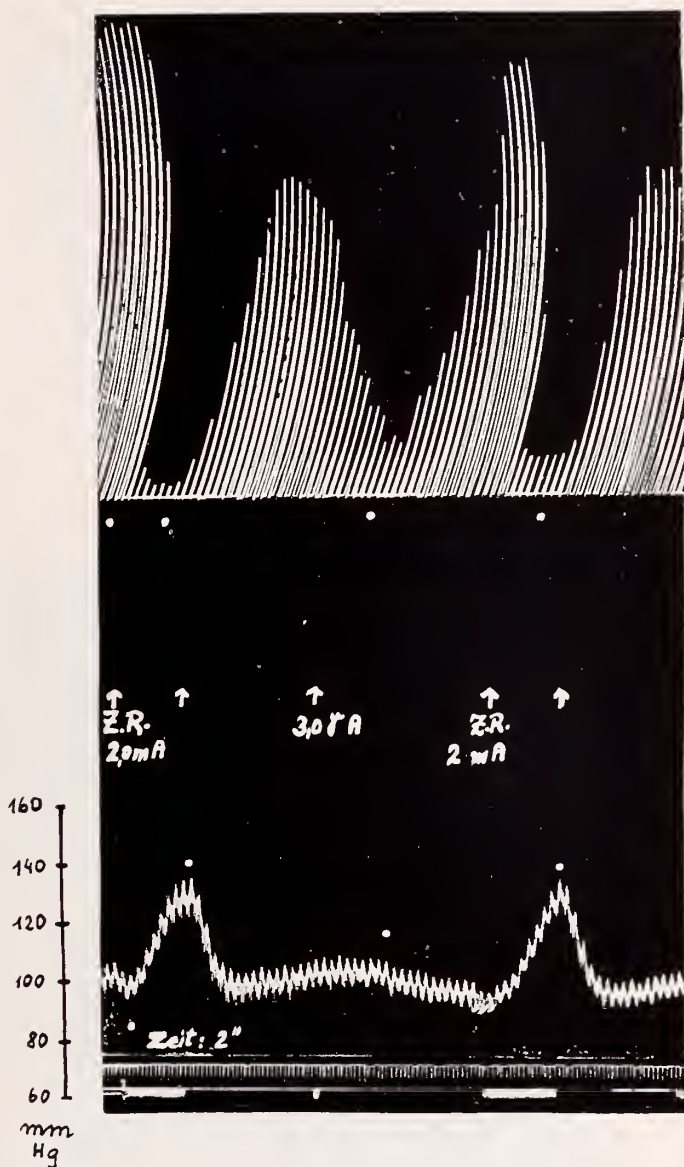


ABB. 2. Registrierung wie in Abb.1. Von Pfeil 1-2 und von Pfeil 4-5. elektrische Reizung des Hypothalamus mit 2mamp. Zum Vergleich bei Pfeil 3. 3,0 g Adrenalin in die vena femoralis.

werden. Es kann demnach nicht das aus der Nebenniere stammende Adrenalin allein sein, welches die broncholytische Wirkung hervorruft. Da es vielmehr möglich war, dass die Broncholyse über den Weg bronchodilatatorischer Fasern

im Sympathikus verlief, haben wir in einem weiteren Versuch beide ggl. stellata mit den ersten 4 bzw. 5 thorakalen Ganglien extirpiert und gleichzeitig beide

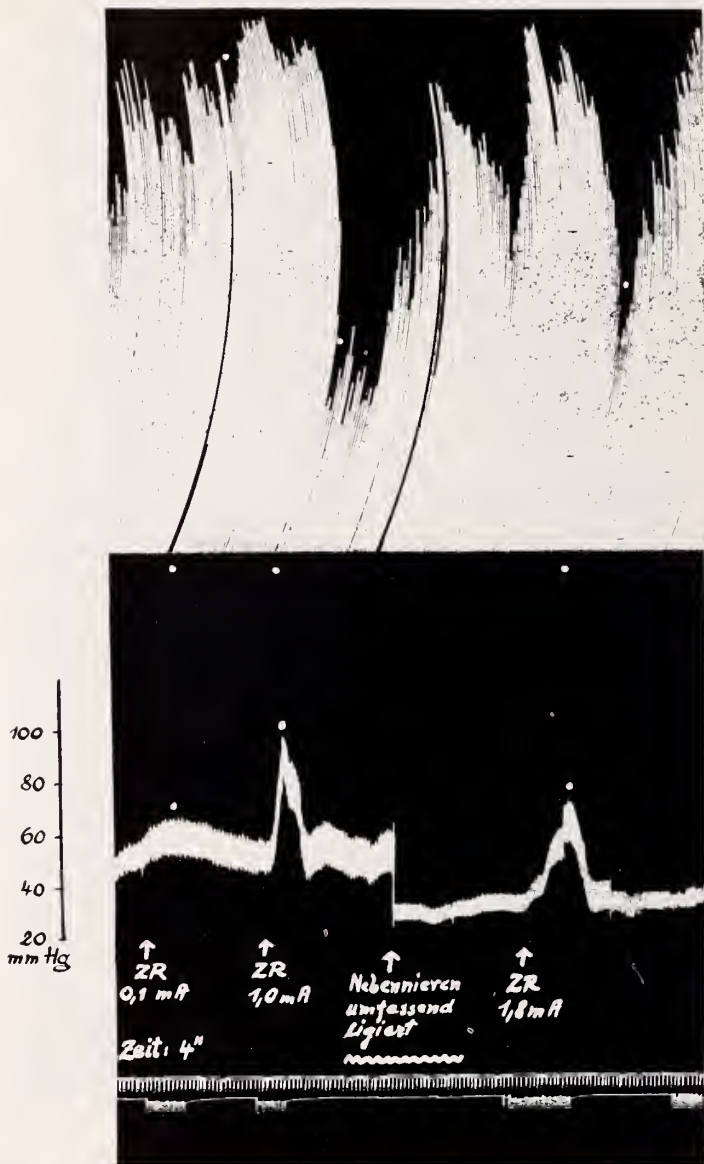


ABB. 3. Registrierung wie in Abb.1.: Beim ersten Pfeil Hypothalamusreizung mit 0,1mamp. bei Pfeil 2 mit 1,0mamp. Dann Abbinden beider Nebennieren. Bei Pfeil 3.) Hypothalamusreizung mit 1,8mamp. Die broncholytische Wirkung der Hypothalamusreizung ist abgeschwächt, aber nicht aufgehoben!

Nn. vagi durchschnitten. Auch nach diesem Eingriff, der zum Mindesten die grösste Zahl der zu den Bronchien ziehenden sympathischen Fasern durchtrennt

haben musste, war sowohl die blutdrucksteigernde, als auch die broncholytische Wirkung der zentralen Reize noch erhalten. Der Effekt kann also auch sicher

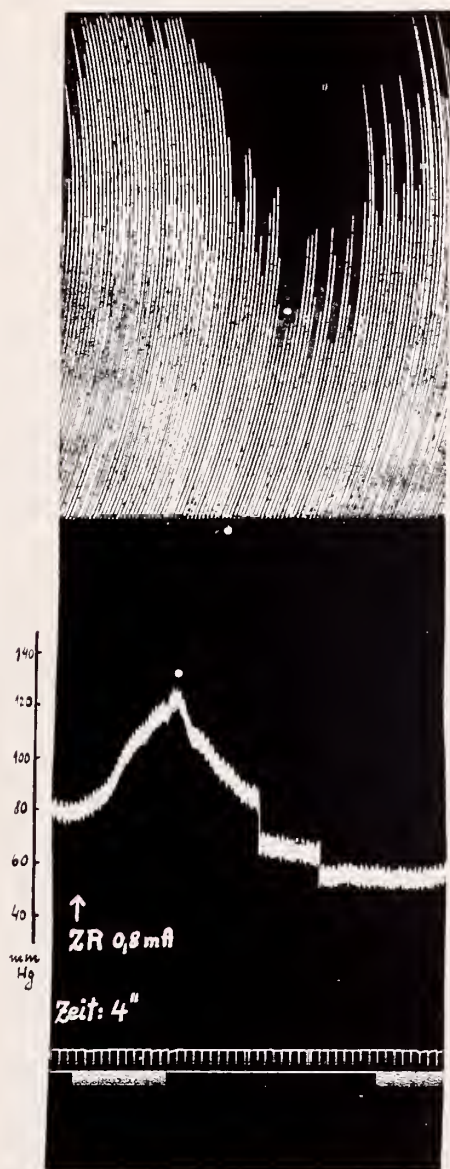


ABB. 4. Registrierung wie in Abb. 1. Beide Vagi sind am Hals durchtrennt, beide Nn. splanchnici reseziert und das Ganglion stellatum sowie die Grenzstrangganglien 1-4 sind extirpiert. Beim Pfeil: Hypothalamusreizung mit 0,8 mAmp. Die broncholytische Wirkung ist noch erhalten.

nicht über bronchodilatatorische Fasern *allein* zustande kommen, die im Sympathikus verlaufen. Wir nehmen demnach an, dass wohl das Inkret der Neben-

niere beim Zustandekommen des Effektes massgeblich beteiligt ist, dass daneben aber auch "Sympathin" eine Rolle spielen mag, dass durch die vom Zentrum ausgehende Erregung adrenergischer Fasern freigesetzt wird.

Anlässlich dieser Versuche haben wir noch ein interessantes Nebenphänomen beobachtet, dass genauer untersucht werden soll: In 6 Versuchen wurde beiderseits der n. splanchnicus vorsichtig präpariert und angeschlungen um ihn später durchtrennen zu können. Es trat nun stets schon nach der Präparation ein deutlicher spontaner Krampf der Bronchialmuskeln ein, selbst wenn vorher kein Pilokarpin gegeben worden war. Auch diese vom sympathischen Nervensystem ausgelöste bronchokonstriktorische Wirkung konnte durch Vagusdurchschneidung und durch zentrale Hypothalamusreizung deutlich gelöst werden.

In einem Versuch wurden 6mg Dibenamin kg intravenös verabreicht, worauf starke Erschlaffung der Bronchien eintrat. Durch eine nachfolgende Gabe von 30mg Pilokarpin wurde deutlicher Bronchospasmus bewirkt. Jetzt trat trotz dreifach höherer Reizstärke keine Blutdrucksteigerung mehr auf und die broncholytische Wirkung der Hypothalamusreizung war etwa auf $\frac{1}{3}$ herabgesetzt. Auch die Wirkung von Adrenalin war in gleichem Ausmass verringert.

Es sei noch erwähnt, dass wir bei einem ganz jungen Hund (8 Wochen alt) bei Hypothalamusreizung stets nur Bronchokonstriktion gesehen haben, ein Effekt, der bei erwachsenen Hunden niemals auftrat.

DISKUSSION

Hebb und Konzett (10) haben an isoliert durchströmten Lungen nachgewiesen, dass Nor-adrenalin etwa 5–10mal schwächer broncholytisch wirkt als Adrenalin. In eigenen Versuchen haben wir gezeigt, dass es bei Hypothalamusreizung zu einer Verschiebung des relativen Gehaltes dieser zwei Hormone im Nebennierenvenenblut kommt: Es wird bedeutend mehr Adrenalin ausgeschieden. Andererseits haben Kaindl und Euler und neuerdings Schümann (11) gezeigt, dass bei Drucksenkung im Carotissinus zwar etwas mehr Gesamtinkret produziert wird, dass jedoch im Wesentlichen bei Katzen Noradrenalin im Nebenniereninkret vorhanden ist. Aber auch abgesehen von dieser Verschiebung in der Zusammensetzung des Inkretes wird bei Hypothalamusreizung erheblich mehr Gesamtkatechol frei als bei Carotidenabklemmung. Es ist daher verständlich, dass wir ebenso wie De Burgh Daly und Schweitzer nie eine broncholytische Wirkung von den Pressorezeptoren des Carotissinus erzielen konnten.

Umgekehrt ist sicher anzunehmen, dass die starke Adrenalinproduktion bei zentraler Sympathikusreizung an der broncholytischen Wirkung beteiligt ist. Diese ist auffallend stark gegenüber den Kreislaufwirkungen ausgeprägt: Aus früheren Versuchen wissen wir, dass auch die glatte Muskulatur des Darmes bei Hypothalamusreizung reagiert, noch bevor der allgemeine Blutdruck nennenswert erhöht ist. Die Bronchialerweiterung geht mit der Darmwirkung durchaus parallel. Wenn wir dazu die ausgeprägte Hyperglykämie nehmen, die bei Hypothalamusreizung entsteht, dagegen nach Versuchen von Brauch (12), Schümann (13) und anderen bei der reflektorischen Sympathikuserregung durch Drucksenkung im Carotissinus völlig fehlt, dann sehen wir, dass die zentrale Sympathikus-

erregung sich in jeder Beziehung ähnlich auswirkt wie eine intravenöse Adrenalinjektion.

Freilich kann die Nebenniere nicht allein, wenn auch vorwiegend für die broncholytische Wirkung verantwortlich gemacht werden. Reizung sympathischer Fasern, die vom ganglion stellatum zur Lunge ziehen hat nicht immer eindeutig bronchodilatatorische Effekte ergeben, so beschreibt z.B. Hebb (14) in älteren Versuchen auch Bronchokonstriktion. Wir haben beobachtet, dass Eingriffe am Sympathikus unterhalb des Abganges der Bronchialäste, also etwa Präparation des Splanchnikus Bronchokonstriktion hervorrufen kann und werden in späteren Versuchen diese Wirkung näher analysieren.

ZUSAMMENFASSUNG

1. Abklemmung beider Carotiden hat keine broncholytische Wirkung auf einen durch Pilocarpin erzeugten Bronchospasmus beim Hund.

2. Elektrische Reizung der mittleren, lateralen Teile des Hypothalamus hat eine stark bronchialerweiternde Wirkung unter gleichen Bedingungen, selbst wenn sie so schwach ist, dass noch kein Blutdruckanstieg erfolgt.

3. Die Bronchialerweiterung bei zentraler Sympathikusreizung tritt auch dann noch auf, wenn beide Nebennieren abgebunden sind, oder beide Nn. splanchnici durchtrennt sind, oder zusätzlich das Ganglion stellatum und die 4 ersten Grenzstrangganglien auf beiden Seiten extirpiert sind.

4. Es wird angenommen, dass die broncholytische Wirkung der Hypothalamusreizung zustandekommt: 1.) Durch im Blute kreisendes Adrenalin aus den Nebennieren, 2.) Durch Sympathin, welches bei Hypothalamusreizung freigesetzt wird und im Blute kreist.

SUMMARY

(1) Clamping of both carotid arteries in the dog (decrease of pressure in the carotid sinus) does not influence the bronchospasm produced by pilocarpine.

(2) Electric stimulation of the midlateral portion of the hypothalamus (sympathetic center) is a powerful bronchial dilator and will break the pilocarpine-induced spasm, even in the absence of concomitant increase of blood pressure.

(3) This broncholytic effect is not influenced by ligatures around both adrenals, cutting of both splanchnic nerves even with additional removal of the stellate ganglia and the sympathetic ganglia Th₁-Th₄ bilaterally.

(4) It is assumed that the broncholytic effect of hypothalamic stimulation is caused by adrenalin derived from the adrenals as well as by circulating sympathin liberated by the stimulation of sympathetic centers.

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DISSEMINATED LUPUS ERYTHEMATOSUS*

(MALIGNANT LUPUS ERYTHEMATOSUS (GOLDSMITH-BEAR))

SEINE GESCHICHTE—VERSUCH EINER BEGRIFFSBESTIMMUNG

L. ARZT

[Wien]

Durch die Arbeiten zahlreicher Forscher, insbesondere in USA, an ihrer Spitze der Pathologe *Klemperer*, ist die unter der ältesten Bezeichnung "Lupus erythematosus"† laufende Erkrankung in den Mittelpunkt des Interesses gerückt worden. Während eines Jahrhunderts fast ausschliesslich von dermatologischer Seite bearbeitet, haben die Pathologen diese Erkrankung in ihr Forschungsgebiet einbezogen, denen sich die internen Kliniker, und in jüngster Zeit ganz im Speziellen die Haematologen, zugesellt haben.

Dieses auf verschiedenen Gebieten der klinischen und theoretischen Medizin sich äussernde Interesse dürfte es rechtfertigen, sich mit der *Geschichte* dieser Erkrankung zu befassen. Daraus werden sich Einblicke dahin ergeben, welche *Symptome* im Laufe der Jahre zu dem Namen Lupus erythematosus führten, und wie durch den Fortschritt der medizinischen Forschung der Begriff Lupus erythematosus einem ständigen Wandel unterworfen war. An diese historischen Reminiscenzen anschliessend, soll abschliessend auch allerdings nur der *Versuch einer Begriffsbestimmung*, nach Mitteilung einer eigenen Beobachtung, angeknüpft werden.

Die Berechtigung für einen solchen Versuch kommt wohl ganz besonders der Wiener medizinischen Schule zu, im besonderen jener Klinik, die historisch mit dieser Erkrankung verbunden ist, da aus ihr vor ungefähr 100 Jahren (1845–1872) die grundlegenden Arbeiten der beiden Vorstände *Hebra* und *Kaposi* veröffentlicht wurden. In einem Festheft, das einer der führenden Persönlichkeiten des medizinischen Wien aus den letzten Jahren vor der Besetzung Österreichs, *Professor E. P. Pick*, dem ehemaligen Vorstand des pharmakologischen Institutes, gewidmet ist, soll in dieser Erinnerung an die grosse Zeit der Wiener medizinischen Schule in den vergangenen Jahrzehnten nur eine *Pflicht der Dankbarkeit* an die verdienten Vorgänger im Amte, unter denen *E. P. Pick* eine führende Stellung einnahm, erblickt werden.

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† *Hebra* und *Kaposi* überschreiben die Abhandlung über diese Erkrankung in ihrem Lehrbuch "Hautkrankheiten" II. Band, Verlag Ferdinand Enke, 1872 im Gesamtwerk "Handbuch der speziellen Pathologie und Therapie," redigiert von Rud. Virchow mit der Bezeichnung "Lupus erythematosus."

Sprachlich ist das Wort erythematosus, das sich aus zwei Sprachen (Griechisch und Latein) zusammensetzt, besser durch erythematoses, das auch weiterhin, soweit es sich nicht um Citate handelt, gebraucht wird, zu ersetzen.

Die *Geschichte* des Lupus erythematosus—so betiteln *Hebra-Kaposi*† in ihrem Lehrbuch diesen Abschnitt—beginnt mit dem Hinweis, dass zuerst Hebra im Jahre 1845 “eine, bis dahin von keinem Autor vorher näher bezeichnete Hautkrankheit in folgender Weise geschildert habe: Seborrhoe congestiva, die meines Wissens nirgends der Natur gemäss beschrieben, und höchstens von *Fuchs* unter dem Namen Seborrhoen adutorum, oder von *Rayer* als Fluxus sebaceus, oder endlich von John *Erichsen* in London, med. Gaz. Nov. 1845 oberflächlich abgehandelt wird.” § Durch die Schilderung “der an den Wangen und der Nase in einer, einem Schmetterling nicht unähnlichen Ausbreitung,” welche “den Anblick einer scharf begrenzten, stark geröteten, mit Schuppen bedeckten, weder juckenden noch nässenden, auch nicht excoriirten Hautstelle” bietet, ist die erste Beschreibung der später vielfach unter dem Namen Schmetterlingsflechte allgemein anerkannten Erkrankung niedergelegt. Die Anreihung der Affektion an den Lupus geschah durch *Cazenave* auf Grund der Feststellung von Narbenbildungen, ebenso die Bezeichnung Lupus erythematosus, welche auch, “durch die gleiche Erfahrung belehrt,” *Hebra* alsbald für diese Erkrankung annahm, und später auch *Kaposi* (1869) gebrauchte.

Im Text zum Atlas der Hautkrankheiten von *Hebra* (1852) ist das grosse Kapitel “Lupus” in 2 Abschnitte getrennt: I. Lupus *Willan*, II. Lupus erythematosus. *Hebra* macht darauf aufmerksam, dass es “*Cazenave*,—dem Schüler *Biett*s, der sich des Namens Érytheme centrifuge bediente,—erst in den Jahren 1850–1891 einfiel, dass sein Lupus érythémateux mit dem Érytheme centrifuge *Biett*s synonym sei.” Zum besseren Verständnis verweist *Hebra* auf die Tafeln VI und VIII mit Abbildungen von Lupus erythematosus im Gesicht, und betont, dass die Erkrankung bis jetzt nur bei Erwachsenen—meist weiblichen Geschlechtes—beobachtet wurde.”

Damit war das lokale Krankheitsbild des Lupus erythematosus festgelegt, wird jedoch schon im *Hebra-Kaposi* schon Lehrbuch dahin ergänzt, “dass auch mannigfache schwere, und, selbst das Leben bedrohende, allgemeine Symptome in innigem Zusammenhange mit dem genannten Prozesse sich einzustellen pflegen, und selbst der Tod unter Verhältnissen erfolgen kann, die als Ausfluss jenes örtlichen Vorganges betrachtet werden müssen.”

Schon in dieser von *Hebra-Kaposi* geschilderten Symptomatologie wird auf den *zweifachen* weiteren Verlauf der Erkrankung besonders hingewiesen. Diese Autoren unterscheiden einerseits einen *discoiden*, und andererseits einen *disseminirten und aggregirten Typus*, für welch letzteren sie den Namen “Lupus erythematosus disseminatus et aggregatus” wählten.

Diese Form ist nach *Hebra-Kaposi* dadurch charakterisiert, “dass sie von Anbeginn aus vielen, getrennt stehenden oder aggregirten Primäreffloreszenzen besteht, und während

† Da dieses Lehrbuch als Autoren *Hebra und Kaposi* ausweist, müssen wohl beide Autoren genannt werden, sodass sich dann sprachliche Veränderungen bei den Citierungen ergeben.

§ Als Literaturangabe wird die Zeitschr. d. K. K. Gs. d. Aerzte in Wien, I. B., pag. 40 angegeben. Wörtlich ist das Citat dem Artikel *Hebra* im Jahresbericht über “die Fortschritte in der Heilkunde im Jahre 1845 von Dr. Cannstatt und Dr. Eisenmann” II. Bd. 1846 entnommen.

des ganzen weiteren Verlaufes nur in der Weise sich ausbreitet, dass die Zahl der Primärefloreszenzen zunimmt. . . .” “Jedoch entwickelt sich auch diese Form des Lupus erythematosus, soweit die bisherigen Beobachtungen dies gelehrt haben,” fahren *Hebra-Kaposi* fort,—“zuerst im Gesicht, und zwar in der Regel *allmählich*, bisweilen aber *acut*, im Verlaufe von nur wenigen Tagen,” wobei die in kurzer Frist auftretenden Veränderungen keineswegs das Bild des Lupus erythematosus zeigen, sondern viel mehr das eines Ekzema acutum impetiginosum. Wieder kommen zwei weitere Entwicklungsmöglichkeiten zur Beobachtung: entweder Bestehenbleiben des regionären Zustandes, oder die Erkrankung kann allgemein werden. Dann erscheinen innerhalb weniger Tage oder Wochen “hunderte von Lupus erythematosus-Punkte zerstreut am Stamm, an den Beuge- und Streckseiten der Finger, der Flachhand, auf den Armen, Ober- und Unterschenkeln, den Ellbogen und Knien, deren Streck- und Beugeseiten, kurz, beinahe über den ganzen Körper zerstreut.”

Die Autoren sprechen dann von einer “akuten oder subakuten Eruption, welche entweder vom Anbeginn der Erkrankung als solche, oder als Exacerbation eines schon bestehenden Lupus erythematosus sich kundgibt,” wobei sie die allgemeinen Erscheinungen im direkten Zusammenhang mit der Eruption, teils wohl als fernstehend, jedoch nicht als blosser Komplikation des Prozesses überhaupt, auffassen.

Unter den “*concomitierenden Erscheinungen*,” die eine acute oder subacute Eruption des Lupus erythematosus begleitet, zählen *Hebra-Kaposi* auf: haselnuss-—bis nussgrosse, tiefe Knoten, Anschwellung der Haut um die Gelenke der Mittelhand, Finger und Zehen, auch Knie und Ellbogen, Knochenschmerzen in den langen Röhrenknochen, Gelenksschmerzen, sogar rheumatische Schmerzen, Hauteruptionen in exanthematischer Form bis zur haemorrhagischen Blasenbildung, auf deren Grund sich “Haemorrhagien des Coriums” finden, eine schmerzhaftes Adenitis, die aber nicht absecdiert, und endlich ein *Erysipel*, bezüglich dessen *Hebra-Kaposi* schreiben: “Der Rotlauf bildet eine häufige und sehr bedenkliche Complication des Lupus erythematosus aggregatus,” bei dem sie zweierlei Formen unterscheiden. Während bei der ersten Form die Erkrankung an solchen Stellen auftritt, welche auch der Sitz der früher geschilderten tiefen, subcutanen, ödematösen Schwellung sind, und von da sich weiter verbreitet und durch seine grosse Ausdehnung auch die Bezeichnung *Erysipelas migrans* verdient, kommt es bei der “zweiten Form zu einer Entwicklung von Rotlauf, welche ich als Erysipelas perstans faciei bezeichnen möchte.” Beide Formen sind von Temperatursteigerungen begleitet, bei der zweiten aber verdient die “gleichzeitige, äusserst grosse Prostration, der typhoide Zustand” eine besondere Beachtung. Schwellung, vor allem die Incrustation, weisen auf einen entzündlichen Prozess hin, der aber durch seine allgemeinen Erscheinungen, wie gestörtes Bewusstsein, ausgezeichnet ist. “Im Verlaufe von 2–3 Wochen,” schreiben *Hebra-Kaposi*, “stellt sich unter zunehmenden Gehirnerscheinungen Koma, Sopor oder Hinzutritt von Pleuro-Pneumonie der Tod ein, oder die entzündlichen Erscheinungen gehen zurück und die Kranken genesen—bis auf den zurückgebliebenen Lupus erythematosus.”

Auch dem Einwand, dass die erysipeloiden Erscheinungen nur eine zufällige Komplikation darstellen, wird von *Hebra-Kaposi* begegnet, indem sie den Lupus vulgaris zum Vergleich heranziehen, bei dem, trotz des häufigen Ätzmittelgebrauches (Lapisstift) das Auftreten eines Erysipels “zu den selteneren Zu-

fällen" gehört. Dagegen fanden sich bei 22 Fällen von Lupus erythematodes darunter 15 weiblichen Geschlechtes,—worauf immer wieder hingewiesen wird,—9 mit wiederholten Erysipelen, und starben im Verlauf desselben 3 Personen. Auch auf Grund der Prognose rechnen *Hebra-Kaposi* alle jene Fälle, welche mit "intensiven lokalen und deletären allgemeinen Erscheinungen" einhergehen, zu ihrer zweiten Form, dem "Lupus erythematosis disseminatus et aggregatus," treten aber trotz der grossen Unterschiede für "eine innige Beziehung beider Lupusformen zueinander" ein, da ihrer Meinung nach "die Primäreffloreszenzen für beide dieselben sind."

Von seiner ersten Bezeichnung "Seborrhoea congestiva" ausgehend, hält *Hebra* an der Vorstellung eines Zusammenhanges mit den Talgdrüsen wohl anfangs fest, wenn er auch ausdrücklich die Häufigkeit beim weiblichen Geschlecht, allgemeine Momente, mittleres Lebensalter, Chlorose, dann aber auch chronischen Katarrh der Lungenspitzen und beginnende Lungentuberkulose erwähnt. Jedoch konnte er sich noch nicht entschliessen, gegen die usuelle Anlehnung des Lupus erythematodes an den Lupus vulgaris vorzugehen, betont aber, dass beide "ihrem Wesen nach vollständig auseinanderzuhalten sind."

Aus den *anatomischen Befunden*, die von *Neumann*, *Geddings* und *Hebra* erhoben wurden, sei auf die Feststellung eines entzündlichen Vorganges um die Talgdrüsen, Haarfollikel und Schweissdrüsen, wobei es zu einer fettigen und wachsartigen Degeneration der betreffenden Elemente kommen kann, hingewiesen. Auch eine "hyaloide Degeneration der Bindegewebelemente des Papillarkörpers," die dann einer "narbigen Einsenkung der Haut" Platz machen, wird von *Hebra* erwähnt.

Schon aus den Ausführungen *Hebra-Kaposi's* ist das Vorkommen zweier Erythematodes Typen ersichtlich, und war nach *P. Veiel Kaposi** der Erste, der diese Formen in eine "ausserordentlich chronische" und in eine "akute, unter Einsetzen heftiger Allgemeinerscheinungen" häufig zum Tode führende, trennte. So einfach und klar diese Trennung erscheint, ergaben sich schon damals nicht selten Übergänge von der chronischen in die akute Form, welche letztere dann mit der *primär* akut beginnenden Form zusammengeworfen wurde. Dieser Schwierigkeit trug *Ehrmann* in seiner Einteilung Rechnung, und unterscheidet: 1.) einen Lupus erythematodes chronicus mit chronischem Verlauf, 2.) einen Lupus erythematodes acutus mit akutem Einsetzen, jene Fälle, die nach *Jadasohn* "den Eindruck der Überschüttung der Haut mit toxischem oder virulentem Material machen," 3.) einen Lupus erythematodes cum exacerbatione acuta: chronische, sich plötzlich akut ausbreitende und meist wieder zur Chronizität zurückkehrende Fälle.

Gegenüber der *chronischen Form* mit zahlreichen *Varianten*, wie ausgesprochen verrucöse, dann wieder lichenoiden und intensiver entzündliche Veränderungen, ja selbst dem Lupus pernio gleichende, oder durch das Auftreten multipler Knoten tumorähnliche Bilder, nimmt der Lupus erythematodes acutus eine *Sonderstellung* ein. Da unter diese Bezeichnung, mangels einer scharfen Ab-

* Schon früher wurde darauf verwiesen, dass für das Lehrbuch "Hautkrankheiten" *Hebra und Kaposi* als Autoren zeichnen, daher eine Unterscheidung nach dem Verfasser jedes einzelnen Kapitels nicht möglich ist.

grenzung, aber die verschiedensten Fälle eingereiht wurden, herrscht auf diesem Gebiet eine *grosse Verwirrung*, worauf ganz besonders schon *Jadassohn* hinwies. So sind Fälle von ausgebreitetem Lupus erythematodes, die zu einer plötzlichen Ausbreitung neigen, bei sonstigem guten Gesundheitszustand des Patienten, nicht mit dem *echten* Lupus erythematodes acutus zu identifizieren. Daher unterscheidet *Veiel*, diesem Umstand Rechnung tragend, 2 Formen; Fälle, bei denen die Erkrankung plötzlich bei schweren Allgemeinerscheinungen "wie ein Blitz aus heiterem Himmel" auftritt, und andere, bei denen sich das akute Geschehen an einen schon bestehenden Prozess anschliesst und die auch in ihrem weiteren Verlauf differieren: fast stets tödlicher Ausgang bei der ersteren, vielfach Besserung bei der letzteren. Diese Beobachtungen waren ja für *Ehrmann* auch der Grund, zwischen einem Lupus erythematosis acutus (Kaposi) und einem Lupus erythematosis cum exacerbatione acuta zu unterscheiden.

Kerl, der sich ganz besonders schon im Hinblick auf die schweren, akut verlaufenden Fälle mit der Einteilung des Lupus erythematodes beschäftigt, geht von 2 Grundformen aus, einer akuten und einer chronischen. Zu der *ersteren*, Lupus erythematodes acutus, zu welcher nur Fälle *ohne Vorausgehen* einer chronischen Form des Lupus erythematosis zählen, rechnet er die Beobachtungen "mit stürmischem Verlauf wie eine Sepsis und zum Exitus führend," dann auch den "Lupus erythematosis subacutus" mit "nicht so stürmischem Verlauf, jedoch ebenfalls ohne Vorausgehen eines Lupus erythematosis chronicus und einem Endausgang mit Restitutio ad integrum oder Übergang in eine chronische Form des Lupus erythematosis.

Schon aus diesen historischen Ausführungen ergibt sich die Notwendigkeit einer *Begriffsbestimmung* und damit einer *präzisen Antwort* auf die Frage: "Was versteht man heute unter Lupus erythematosis acutus?"

Da im allgemeinen bei einer solchen Entscheidung eine eindeutige Feststellung der *Ätiologie* die sicherste Antwort geben würde, soll als erstes auf die Frage der *Ätiologie* eingegangen werden.

Wenn *Hebra* auch zu Anbeginn von der Vorstellung eines hyperaemischen Vorganges im Zusammenhang mit den Talgdrüsen befangen war—daher seine aber alsbald aufgegebene Bezeichnung "Seborrhoea congestiva"—, wurde, wie die durch Jahre hindurch allgemein verwendete Bezeichnung Lupus erythematodes besagt, ein *Zusammenhang* mit dem Lupus vulgaris, vor allem hinsichtlich einer *tuberkulösen Ätiologie*, angenommen. Allerdings heisst es im *Hebra-Kaposi*'schen Lehrbuch wörtlich: "Wir sind nicht in der Lage, Daten über die Ursache des Lupus erythematosis anzugeben." Besonders um die Jahrhundertwende fand die tuberkulöse Ätiologie vielfach Anerkennung, doch wurde ein wirklich allen Einwänden standhaltender Beweis für die tuberkulöse Ätiologie des Lupus erythematodes, was besonders *Jadassohn* betont, bisher nicht erbracht, und auch eine angenommene Infektätiologie im weitesten Wortsinn, darunter eine eventuelle Virusinfektion, hielt Nachprüfungen nicht stand. Damit wurde aber auch eine Begriffsabgrenzung auf Grund der *Ätiologie* zur *Unmöglichkeit*. Wenn daher dieser Tatsache entsprechend die Bezeichnung "Lupus" von vielen Autoren

als zu falschen Vorstellungen führend abgelehnt und nur von "Erythematodes" gesprochen wird, kann diesem Standpunkt nur zugestimmt werden.

Diese historische Zusammenstellung zeigt, dass bisher für die *Diagnose allein klinische Momente*, sowohl in den Hauterscheinungen selbst gelegen als auch in dem Gesamtzustand des Kranken gegeben, verwertet werden konnten.

Da nun die klinischen Krankheitsbilder der einzelnen Fälle sich nicht vollkommen gleichen, ist der Wert einer *zusammenfassenden Symptomatik* davon abhängig, *welche Fälle* zum Erythematodes gezählt werden. Eine diesbezügliche Differenz, die sich dann bei dem Versuch einer Begriffsbestimmung erschwerend auswirken muss, liegt auch in der Einteilung, wie sie *einerseits* von *Ehrmann*, *andererseits* von *Kerl* aufgestellt wird, vor. Denn während *Kerl* bei seiner *akuten Grundform* des Erythematodes zwei Varianten, je nach dem Verlauf, den Erythematodes acutus und subacutus, unterscheidet, jedoch für beide die Forderung aufstellt, dass *kein* Lupus erythematodes chronicus *vorausging*, basiert die Einteilung *Ehrmanns allein* auf dem momentan vorliegenden Krankheitsbild, und wird ein eventuell vorausgegangener Erythematodes ausser Acht gelassen.

Es mag vielleicht auffallend sein, dass bei der Diagnose des Erythematodes im allgemeinen bisher von den Ergebnissen der *histologischen Untersuchungen* der Hautveränderungen nicht gesprochen wurde. Allerdings haben schon *Hebra-Kaposi* eine hyaloide Veränderung im Bindegewebe erwähnt. Aber da es nicht möglich war, aus diesen fast 80 Jahren zurückliegenden Angaben sich ein Bild zu machen, und spätere Untersuchungen anderer Autoren auch kein für Erythematodes *pathognomonisches* Bild vermittelten, wurde der Weg der histologischen Diagnose verlassen. Die zuerst von *Hargrave* und seinen Mitarbeitern im Knochenmark gefundenen eigenartigen Zellen, und besonders die durch *Haserick* nach Anreicherungsverfahren im peripheren Blut nachgewiesenen L. E. Zellen stellen zweifelsohne einen wesentlichen Fortschritt dar, doch ist die so verheissungsvolle Forscherarbeit keineswegs schon abgeschlossen.

Es war nun das Verdienst *Klemperers* und seiner Mitarbeiter, den Grundsätzen *Morgagnis* folgend, auf der Suche nach dem *Sitz der Erkrankung*, bestimmte, für den akuten Erythematodes charakteristische Befunde bei einer grossen Zahl von ad exitum gekommenen Fällen erhoben zu haben. Da *Klemperer* vor allem *Veränderungen im Bindegewebe*, und zwar in den *kollagenen Fasern und Bündeln* fand,—aber nicht nur beim akuten Erythematodes, sondern auch bei der Sklerodermie, der Dermatomyositis, der Periarteriitis nodosa u.a.—fasste er alle diese Erkrankungen zusammen und bezeichnete sie als Kollagenosen, "Diffuse Collagen Disease." Er erblickte darin eine *Systemerkrankung*, bei welcher das Bindegewebe in seiner Gesamtheit (entirety) befallen ist, wodurch schon von vorneherein die nur lokalen Fälle von Erythematodes ausscheiden. Daher müssen also in erster Linie jene Fälle, die von *Kerl* in seine erste Grundform "Erythematosis acutus" gerechnet werden, Beachtung finden, für deren Sonderstellung die Forderung *Kerls*, das Nichtvorausgehen eines Erythematosis chronicus, Voraussetzung ist. Es scheint aber doch auch wieder berechtigt, auf Grund der *Ehrmann'schen* Einteilung nicht nur die als Erythematodes acutus, sondern wohl auch die von ihm als Lupus erythematosis cum exacerbatione acuta bezeichneten Beobachtungen hieher zu zählen. Sonach besteht zwischen

den Ansichten *Ehrmanns* und *Kerls* wohl eine *Differenz*, die aber von pathologisch-anatomischer Seite wohl kaum in Zukunft als ausreichend für eine Unterscheidung angesehen werden dürfte. Denn es ist ja z. B. aus einer jüngst erschienenen Arbeit von *Neuhold* und *Wolfram* ersichtlich, dass auch, zumindest in manchen Fällen von *Lupus erythematodes disseminatus cum exacerbatione acuta*, ja selbst in Fällen von *Lupus erythematodes discoides cum exacerbatione acuta* sich die gleichen Gewebsveränderungen weit verbreitet im kollagenen Gewebe finden können.

Wenn also schon *Klemperer* und seine Mitarbeiter auf der einen Seite eine Begrenzungslinie gegenüber dem lokalen Erythematodes ziehen, da sie ja für die hieher zu zählenden Fälle eine Erkrankung des Bindegewebes in seiner *Gesamtheit* voraussetzen, gehen andere Autoren in der entgegengesetzten Richtung wesentlich weiter. So veröffentlichten *Rakov* und *Taylor* (1942) unter dem Titel "*Acute disseminated lupus erythematosus*" einen Fall, bei dem *Hautveränderungen überhaupt fehlten*. Schon *Ginzler* und *Fox* (1940) haben diese *Möglichkeit* vertreten, die auch von *Rost* (1948) als sehr wahrscheinlich angesehen wird. Solche Fälle jedoch unter dem Titel "*Erythematodes*" zu führen, kann wohl nicht ohne Einschränkung beigeprlichtet werden, da ja damit die geschilderte historische Entwicklung dieser Erkrankung, aber auch ethymologisch die Bezeichnung "*Erythematodes*," die sich doch nur auf Hauterscheinungen—wenn auch ausserordentlich mannigfaltige—beziehen kann, nicht in Einklang zu bringen ist. Ob aber solche Fälle mit dem *völligen Fehlen von Hauterscheinungen*, und zwar während des ganzen Krankheitsverlaufes, zu den Kollagenosen im Sinne *Klemperers* zu rechnen sind, wird von pathologisch-anatomischer Seite entschieden werden müssen.

Auf Grund dieser Erwägungen käme man also wieder zu dem Schluss, 2 *Grundformen* des Erythematodes aufzustellen, eine *chronische* und eine *akute*. Für die chronische Grundform wäre als markantester Vertreter der *Lupus erythematosus chronicus discoides* in der so bekannten Schmetterlingsform anzusehen. Dagegen käme die akute Grundform in jenen Fällen am prägnantesten zum Ausdruck, bei denen "wie ein Blitz aus heiterem Himmel" (*Judasohn*) das schwere Allgemeinkrankheitsbild in Erscheinung tritt, begleitet von entzündlichen, mächtig exsudativen, besonders im Gesicht aber auch an den Händen lokalisierten Hautveränderungen, teils nässend, sehr rasch aber auch von Blutkrusten bedeckt, vielfach auch von ausgedehnten Blutungen in die Haut und entzündlichen Veränderungen an der Mundschleimhaut und Konjunktiva begleitet.

Von diesen 2 skizzierten, typischsten Vertretern der beiden Grundformen werden nun in einzelnen Fällen zahlreiche *Varianten* beobachtet. Vielfach sind in diese Abweichungen vom typischen Bild nur *graduelle Unterschiede* zu erblicken, wie ja schon *Kerl* bei der akuten Grundform von einem *Erythematosis acutus* und einem *Erythematosis subacutus*, je nach dem Verlauf und dem Endausgang—Exitus beim ersteren, *Restitutio ad integrum* bei letzterem—spricht.

Analoge *Abweichungen* werden auch bei der chronischen Grundform beobachtet, in der sich bei bestehendem discoiden Typus ein *Lupus erythematodes discoides cum exacerbatione acuta* und ein *Lupus erythematodes discoides cum exacerbatione subacuta* ausbilden kann.

Da aber *Kerl* noch eine zweite Type des chronischen Lupus erythematodes, den Erythematodes chronicus disseminatus, anerkennt, trennt er wieder in einen Lupus erythematodes chronicus disseminatus cum exacerbatione acuta und einen Lupus erythematodes chronicus disseminatus cum exacerbatione subacuta. Jedoch ist die Bezeichnung der Verlaufssart—akut oder subakut—nicht massgebend für die Zuteilung eines solchen Falles zur entsprechenden Grundform, sondern sieht *Kerl* das in dieser Hinsicht entscheidende Kriterium im *Fehlen des Vorausgehens einer chronischen Form* des Erythematodes.

Bei Beipflichtung zur *Kerl'schen* Ansicht drängt sich aber die Frage auf: Was hat dieser Erythematodes acutus—die akute Grundform im Sinne *Kerl's*—in seinem klinischen Bild und in seinem Verlauf überhaupt noch mit dem Lupus erythematodes chronicus (der chronischen Grundform), sei es nun der typische „discoides“ oder der, von *Kerl* auch dazu gerechnete „disseminatus,“ noch für einen Zusammenhang? Ist es vielmehr nicht nur gerechtfertigt, ja sogar geboten, diese beiden Grundformen, akute und chronische, vollkommen voneinander als *zwei selbständige Erkrankungen* zu trennen? Auch *Rost* hat schon zu dieser Frage Stellung genommen, und sieht in einer solchen Trennung nur eine grobe Schematisierung, da aus der „chronischen Form gelegentlich sich eine akute entwickeln kann,“ „also enge patho-physiologische Beziehungen zwischen beiden Formen bestehen.“

Die *Gegenargumente*, welche einer solchen Trennung entgegengehalten werden können, sind doppelter Art: einmal, dass tatsächlich, wenn auch selten, das Krankheitsbild des Lupus erythematodes discoides cum exacerbatione acuta, also der chronischen Grundform im Sinne *Kerl's* zugehörig, mit Veränderungen in den inneren Organen den Kollagenosen *Klemperers* entsprechend (Fall II von *Neuhold und Wolfram*) zur Beobachtung kommt, ferner, dass wieder umgekehrt auch die „chronische Grundform“ in der *Variante der Dissemination* mit akuter Exacerbation dem Krankheitsbild der „akuten Grundform“ weitgehend gleichen kann. Zweifelsohne bestehen also im klinischen Bild *Übergänge*, die im einzelnen Fall eine *Trennung ausserordentlich erschweren*. Auch die besten Kliniker der vergangenen Decennien haben insoferne geirrt, als sie Fälle zum Erythematodes acutus rechneten, die im Sinne *Kerl's* einen akuten Verlauf nach bereits vorher bestandenen discoiden Herden zeigten. Solche *Zwischenformen* und *Übergangsbilder* sollen an einer *eigenen Beobachtung* gezeigt werden.

Eine 38 jährige Frau—aus Vorgeschichte sei nur eine Gonitis vor 18 Jahren erwähnt—erkrankte nach einer Sonnenbestrahlung im Sommer 1944 mit roten, symmetrischen Flecken an beiden Wangen. Nach einigen Wochen ohne ärztliche Hilfe Heilung. Bis 1947 erscheinungsfrei, bis auf rezidivierende Eiterungen an den Fingerspitzen. Juni 1947 nach Sonnenbestrahlung wieder erythematöse Herde an beiden Wangen. I. Spitalsaufnahme: Herpes labialis mit Fieber, Rötung und Schwellung des Gesichtes, dann Nässen und Krustenbildung, blutige Stühle, im Harn Spuren Porphyrin. Nach 8 Millionen E. Penicillin erscheinungsfrei. Ende Juli 1949 II. Spitalsaufnahme mit ebensolchen Hauterscheinungen; Abheilung auf 6 Mill. E. Penicillin, erscheinungs- und beschwerdefrei. III. Spitalsaufnahme Mai 1951. Nach kurzer Sonnenbestrahlung gleichartige entzündliche Erscheinungen im Gesicht, begleitet von erythematösen Herden an den Volae manus, Beugeseiten der Finger, an den Fusssohlen und in der crena ani. Fieber, rascher Gewichtsverlust. Juli 1951 sowohl nach Einwirkung von Blutplasma auf normales Knochenmark, dann auch im Blut selbst Lupus erythematodes Zellen zu finden. (Doz. Fleischhacker). Da Behandlung mit Penicillin ohne Erfolg, zuerst intramusculär, dann intravenös ACTH in der Gesamtmenge

von 1140 mg. Am 25. VIII. nach Abheilung der allgemeinen Erscheinungen und der lokalen Hautveränderungen entlassen. Kontrolle am 31. X. 1951. Sowohl im Plasma plus normalen Knochenmark als auch im Citratblut Lupus erythematodes Zellen zu finden. Blutsenkung 96/120.

In diesem Fall dauerte es, von den ersten Erscheinungen im Jahre 1947 bis zum Ausbruch eines schweren Ausbruches von Lupus erythematodes disseminatus im Frühsommer 1951, drei Jahre. Durch die eingeleitete Therapie gelang es zwar, klinisch eine weitgehende Besserung, jedoch bei bleibendem positiven Befund von Hargraves Zellen und einer stark erhöhten Senkungsgeschwindigkeit zu erzielen. Da ein vorausgehender Lupus erythematodes discoides nicht nachzuweisen war, ist der Fall trotz des atypischen Verlaufes, zum akuten Lupus erythematodes disseminatus, sowohl nach *Ehrmann* als auch nach *Kerl*, zu rechnen. Bei Betrachtung des bisher durch 4 Jahre beobachteten Krankheitsverlaufes sind wohl die zwei ersten Ausbrüche als Vorläufer der, im Frühsommer 1951 schweren, aber bisher nicht tödlich verlaufenden Erkrankung anzusehen.

Aber alle diese Erwägungen bestehen nur dann zu Recht, wenn man den *Tatsachen*, verleitet durch Jahre hindurch herrschende Ansichten, in dem Sinne *Gewalt antut*, dass man alle erörternden Beobachtungen unbedingt als zusammengehörig, also als eine *Einheit*, wenn auch im weitesten Sinne, ansieht. Folgerichtig wird man dann auch diese Fälle mit dem gleichen Wort—und es ist ja nur ein Wort, dessen Begriff zu finden der Zweck vorliegender Arbeit ist—“Lupus erythematodes,” oder besser, da die Verwendung des Wortes Lupus aus schon erwähnten Gründen allgemein abgelehnt wird, “*Erythematodes*” *allein*, zusammenfassen.

Nun wurde schon erwähnt, dass *Rakov* und *Taylor* (1942) zum akuten Erythematodes auch ihren Fall rechnen, bei dem Hautveränderungen überhaupt fehlen. Wenn man auch gewiss berechtigt ist, auf Grund des pathologisch-histologischen Befundes, dem ja eine entscheidende Bedeutung zukommt, ihre Beobachtung den Kollagenosen zuzuzählen, so führt, wie schon ausgeführt, eine *Bezeichnung als “Erythematodes”* aus historischen und ethymologischen Gründen zu einer *Begriffsverwirrung*. Alle diese Widersprüche kommen bei der, von *Klemperer* und seinen Mitarbeitern gewählten und histologisch fundierten Bezeichnung *Kollagenosen* in Wegfall, da sie differierende, klinische Bilder von Erkrankungen des Gesamtorganismus durch ein einigendes Band, die eigenartigen Bindegewebsveränderungen, zusammenfassen. In die Gruppe der Kollagenosen nach *Klemperer* fallen somit jene Fälle von Erythematodes, die *Kerl* seiner akuten Grundform zuzählt, aber auch der eine oder andere Fall, dessen derzeitige Erscheinungen und Verlauf, obwohl ein chronischer lokalisierter Prozess einmal voranging, die Zurechnung bei weit verbreiteten Veränderungen im kollagenen Gewebe rechtfertigt; schliesslich ist auch die Einreihung jener Fälle, denen Hautveränderungen zwar völlig fehlen, bei Voraussetzung eines entsprechenden Verlaufes und der charakteristischen Veränderungen im Kollagen, berechtigt.

Diese von *Klemperer* erhobenen histologischen Bilder, im Einklang mit den klinischen Tatsachen, gestatten den *Versuch einer Begriffsabgrenzung des Syndroms Erythematodes disseminatus acutus (malignant lupus erythematosus)*, wobei als Grundlage weitgehendst die *Zusammenfassung Tappeiners* dienen soll: Eine

schwere, plötzlich einsetzende *Allgemeinerkrankung* von *septischem Verlauf* mit *polymorphen Hauterscheinungen*, teils einem Erythema multiforme, teils einem septischen Exanthem gleichend, sowohl im Gesicht als auch an Stamm und Extremitäten, vielfach auch von *Mundschleimhautveränderungen* begleitet, dabei eventuell auch *entzündliche Mitbeteiligung der serösen Häute*, wie Endocarditis, Pericarditis, Pleuritis, Arthritis oder auch eine *Nephritis*, nur ganz vereinzelt auch nach einem bereits bestehendem, lokalisiertem Erythematodes (z. B. Fall II von Neuhold und Wolfram) einsetzend, fast ausschliesslich bei Frauen, vielfach mit *Hargrave-Haserick Zellen im Blut* (Knochenmark), meist *tödlichem Ausgang*, und, post mortem histologisch nachweisbarer allgemeiner *Kollagenose* (*Klemperer*) in den inneren Organen, eventuell auch in den Hautveränderungen. Die *Differenz* mit der von *Tappeiner* aufgestellten Begriffsbestimmung besteht, neben der Erwähnung der, in den letzten Jahren erhobenen und ausgebauten *Blutbefunde*, nur hinsichtlich der zugestandenen *Möglichkeit einer plötzlichen Entwicklung der akuten Form auch bei vorausgegangenem chronischen Erythematodes*. Damit ist allerdings die scharfe Trennung *Kerls* in seine zwei Grundformen (akute und chronische) nicht mehr generell aufrecht zu erhalten.

Wenn auch damit eine Gruppe bestimmter, bisher unter dem Namen Erythematodes laufender Fälle eine, der Kritik standhaltende *Zusammenfassung* auf Grund der Veränderungen im kollagenen Gewebe, erfährt, so kann dies für den praktischen Gebrauch des Klinikers nicht als befriedigend bezeichnet werden. Denn in die Gruppe der Kollagenosen werden seit *Klemperers* Feststellung ja noch eine Reihe weiterer, mit Hautveränderungen einhergehende Erkrankungen, wie die allgemeine Sklerodermie, die Dermatomyositis, die Periarteriitis nodosa, die akuten rheumatischen Infekte etc., gezählt. Alle diese Krankheitsnamen aufzugeben kann deswegen nicht berechtigt empfohlen werden, weil sie, seit langem eingebürgert, mit diesem Namen ein bestimmtes klinisches Bild vermitteln und dadurch auch den zweiten Zweck jeder Bezeichnung, neben der Vermittlung einer bestimmten Vorstellung dem gegenseitigen Verständnis zu dienen, erfüllen.

Eine solche Bezeichnung darf einerseits nicht mehr das Wort "*Lupus*", als ätiologisch nicht zutreffend, enthalten, andererseits aber muss sie auch die Beifügung "*erythematosus*", mit Rücksicht auf das Vorkommen teils vollkommen andersartiger, oder auch gänzlich fehlender Hautveränderungen, aufgeben.

Somit wird es, bis eine neue Bezeichnung gefunden wird, was wohl bei dem derzeitigen Stand unserer Kenntnisse vor allem Aufgabe der Pathologen sein wird, zweckmässig sein, diese Lücke durch einen teilweise umschreibenden Ausdruck zu füllen, wie: "*Kollagenose unter dem Bilde eines Erythematodes*, eventuell auch einer Sklerodermie, Dermatomyositis etc.," jedoch bei seltenen Fällen ohne jede Hautveränderungen nur die Gruppenbezeichnung "*Kollagenose*" zu gebrauchen.

SUMMARY

After a review of the historical development of our knowledge of lupus erythematosis, the author points to some of the recent changes in the concept of this disorder, based primarily on the work of Klemperer and his school.

These changes make it desirable to replace the now obsolete name of the disorder. The noun "lupus" should be reserved for a form of cutaneous tuberculosis as suggested by numerous authorities, while the adjective "erythematosus" or preferably "erythematoses" will be found inadequate for all those cases where types of eruption other than erythema appear or where there is no skin involvement.

Some new name will have to be found as our knowledge of this and related disorders increases. In the meantime it may seem appropriate to classify cases as "collagenosis presenting as erythematoses" or "presenting as scleroderma" etc. as the case may be. The occasional case devoid of skin lesion would then be called "collagenosis" without further qualification.

An illustrative case report is included which concerns a recurrent disseminated variant of this disorder. The patient is still alive after having had three episodes during four years.

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UEBER DIE NEUROGENE APPENDICOPATHIE*

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Es sind genau 30 Jahre vergangen, seitdem R. Maresch durch eine nur kurze, wenige Seiten umfassende Veröffentlichung die Aufmerksamkeit der Aerzte auf das Verhalten der nervösen Elemente im Wurmfortsatz gelenkt hat. Maresch war es aufgefallen, dass die mikroskopische Untersuchung der Appendix in Fällen, welche klinisch das Bild chronisch-recidivierender, offensichtlich von seiten der Appendix ausgehender Schmerzattacken geboten hatten, die Appendix durch ein Füllgewebe verschlossen erwies, das nicht die feingeweblichen Kennzeichen einer chronischen Entzündung zeigte, wie dies nach dem klinischen Bilde zu erwarten gewesen wäre. Trotz dieses hinsichtlich einer Entzündung negativen histologischen Befundes war die Entfernung des Wurmfortsatzes insoferne erfolgreich zu werten, als die Patienten von ihren Schmerzen befreit waren.

Diese Diskrepanz zwischen klinischer Symptomatologie und dem mikroskopischen Befund wusste Maresch dadurch zu klären, dass er, in dem an Stelle der Wurmfortsatzlichtung getretenen Füllgewebe eine *Wucherung nervöser Elemente* nach Art "neuromartiger Bildungen" nachzuweisen vermochte. Er stellte sie den von Stoerk im Grundgewebe callöser Magengeschwüre nachgewiesenen gewucherten Nervenstämmchen an die Seite, welche letzterer Autor mit Amputationsneuromen verglichen hatte.

In einer im gleichen Jahre—1921—erschienenen umfangreichen Publikation, in welcher er auch auf die Beobachtung Mareschs hinweist, beschäftigte sich der damals noch in Strassburg tätige französische Pathologe P. Masson eingehend mit dem Verhalten des Nervengewebes im Wurmfortsatz. Masson kam zu dem Schluss, dass diese neuromartigen Wucherungen in engen Beziehungen zu den sogenannten argentaffinen Zellen der Drüsen der Appendixmucosa stehen, da er oft inmitten derartiger Nervenfaserverwucherungen argentaffine Zellen feststellen konnte.

Seit diesen beiden ersten Mitteilungen scheint diese "neurogene Appendicitis" etwas in Vergessenheit geraten zu sein und vor allem im anglo-amerikanischen Schrifttum einem gewissen Skeptizismus auch noch in neuerer Zeit zu begegnen, vor allem hinsichtlich der klinischen Bedeutung dieser mikroskopischen Veränderungen. So schreibt z. B. Boyd 1947 "it is not possible to say at present what is the exact clinical significance of these histological observations" und weiter "further work on the correlation between these pathological findings and the clinical course is much needed." Auch Moore scheint nicht völlig von der Bedeutung dieser Nervengewebswucherungen überzeugt. Demgegenüber ist in Europaischen Ländern, vor allem seit durch die Untersuchungen von de Castro, Stöhr jr., Boeke, Feyrter, Coronini und vielen Anderen die Aufmerksamkeit der Pathologen auf das "nervöse Terminalreticulum" gelenkt worden ist, diesen Veränderungen in der Appendix nicht bloss lebhaftes Interesse geschenkt,

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sondern auch eine entsprechende Bewertung hinsichtlich der klinischen Symptome zuteil geworden.

Ueber die seinerzeitigen Feststellungen Mareschs hinaus wissen wir heute, dass auch ohne Obliteration der Appendix eine recht erhebliche Wucherung des nervösen Endabschnittes vorhanden sein kann. Ein auffallender Reichtum an eosinophilen Leukocyten kann bei sonst scheinbar unversehrter Schleimhaut schon als ein Hinweis auf eine "neurogene Appendicitis" gewertet werden, ebenso eine Vermehrung der argentaffinen Zellen in den Drüsen, was oft mit den von Masson als "bourgeonnement" bezeichneten Knospungen dieser Zellen gegen das Stroma zu vergesellschaftet ist. Die Wucherung der nervösen Elemente ist auch oft ohne Specialfärbungen, als welche vor allem Silberimprägnationen in Frage kommen, im gewöhnlichen Haematoxylin-Eosinpräparat daran zu erkennen, dass in der Mucosa infolge ihrer Kernarmut heller erscheinende Areale zu sehen sind, die bei stärkerer Vergrösserung sich als aus einem ungemein zarten, feinfibrillären Netzwerk aufgebaut erweisen, wobei mit den gebräuchlichen Bindegewebisfärbungen an diesen Stellen sich nur gröbere collagene Fasern, nicht aber diese erwähnten feinsten oft netzartig angeordneten Fäserchen darstellen lassen. In neuerer Zeit hat Lassmann durch ein etwas modifiziertes Versilberungsverfahren diese feinsten Fibrillen sehr anschaulich wiedergeben können. Sie entsprechen nicht den gewöhnlichen Neuriten, sondern den feinsten Ausläufern des nervösen Endapparates und stehen offensichtlich mit dem Nervenplexus der Mucosa in genetischer Beziehung, wie dies schon seinerzeit Maresch ausgesprochen hat. Unter dem Einfluss dieser nervösen Wucherungen schwinden allmählich die praeexistenten Elemente der Mucosa, am längsten, wie dies auch Lassmann hervorhebt, leistet das Lymphatische Gewebe Widerstand, das man denn auch häufig noch in Form kleinerer oder grösserer Ansammlungen in dem schliesslich verödeten Wurmfortsatz antreffen kann. Analoge Wucherungsvorgänge nehmen von dem Meissnerschen Plexus ihren Ausgang und auch der Auerbachsche Plexus zeigt Hyperplasie der Ganglienzellen, welche oft mehrere Kerne besitzen können und in deren unmittelbarer Umgebung finden sich sehr reichlich feinste unregelmässig sich durchflechtende, netzartige Faserbildungen. Die innere Schicht der Muskularis propria erscheint dadurch dissociiert, während die äussere Lage derselben nichts auffallendes zeigt.

Wohl aber bieten die *kleinen arteriellen Gefässe*, sowohl in obliterierten, wie auch in ein deutliches Lumen zeigenden Appendices ein eigentümliches Verhalten.

Dieselben erscheinen, wie Abb. 1 zeigt, auffallend dickwandig, sodass sie bei oberflächlicher Betrachtung zunächst als atherosklerotisch verändert imponieren können. Begegnet man derartigen Bildern bei Jugendlichen, so wird man berechnigte Zweifel an der Richtigkeit dieser Vermutungsdiagnose hegen dürfen. Dies um so mehr als der Schweizer Pathologe Reubi diese Wandverdickung der kleinen Arterien als Ausdruck einer Wucherung der nervösen Elemente dieser Gefässe, als eine *Angio-Neuromatose* erkannte, die er ebenso wie Obiditsch-Mayer und Feyrter in Fällen von Recklinghausenscher Neurofibromatose beobachtet hat. Wir haben diese eigentümliche Gefässveränderung in unseren Fällen

von "neurogener Appendicitis" sehr häufig gesehen, wobei dieser Gefässprozess manchmal sogar stärker in die Augen fallend war, als die anscheinend erst im Beginne stehende, abseits der Gefässe vorhandene Wucherung des nervösen Endnetzes. Wir möchten dies besonders hervorheben, da unseres Wissens diesen Gefässveränderungen in der Appendix nicht die ihnen, wie wir glauben, gebührende Beachtung geschenkt worden ist. Inwieferne derartige Gefässveränderungen mit den Ricker'schen Anschauungen über die dominierende Rolle der terminalen Strombahn, dem "Telerrheithron," in Uebereinstimmung stehen, sei hier nicht weiter erörtert.

Gewissermassen als Kulminationspunkt dieser Wucherungen des nervösen Endnetzes stellen sich dann die bereits 1921 von Maresch entdeckten kleinen

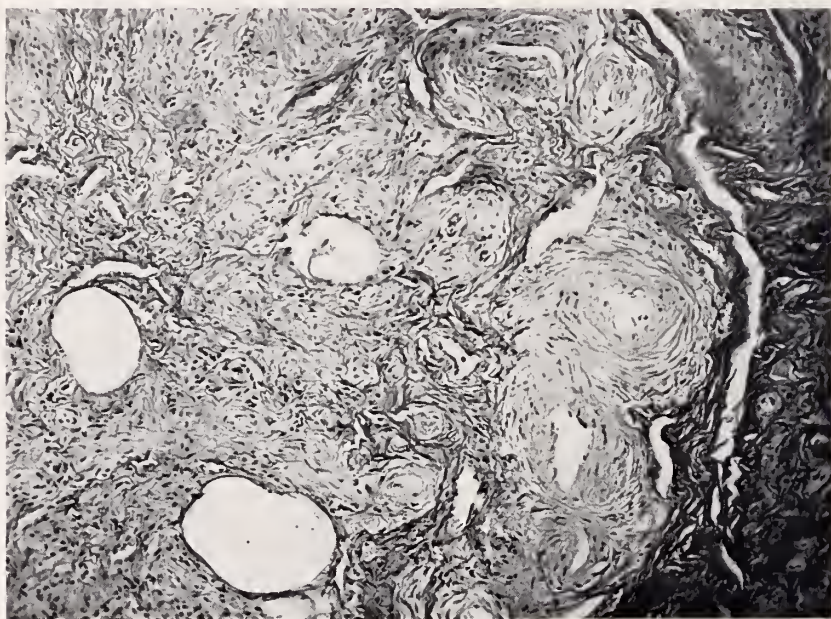


ABB. 1. Angio-neuromatose bei neurogener Appendicopathie

Neurome dar, die, auch in der Vielzahl vorkommend, (Boyd) so augenfällig sind, dass ihr Nachweis die ganze Frage der "neurogenen Appendicitis" in's Rollen gebracht hat. In Abbildung 2 ist ein Originalpraeparat von Maresch wiedergegeben, das in der Sammlung des Wiener Institutes verwahrt wird.

Die Tatsache des Bestehens einer "neurogenen Appendicitis" kann somit heute wohl nicht mehr angezweifelt werden. Wir möchten dabei als *offene Form* jene Fälle bezeichnen, in denen noch ein Appendixlumen vorhanden ist, als *geschlossene Form* aber jene, in denen die Appendix obliteriert ist. Da aber das sonst entzündliche Vorgänge characterisierende feingewebliche Bild fehlt, möchten wir nicht von einer "neurogenen Appendicitis" sondern von einer *neurogenen Appendicopathie* sprechen.

Eine derartige neurogene Appendicopathie ist nach unseren in Wien gewon-

nenen Erfahrungen ein nicht so seltenes Vorkommnis. Wir haben unter 1249 operative entfernten Wurmfortsätzen, welche während des Jahres 1950 dem Wiener pathologisch-anatomischen Institute eingesandt worden waren, 84 mal diese Bilder gesehen. In allen diesen Fällen hatte die klinische Diagnose "chronische Appendicitis" gelaute, woraus hervorgeht, dass gewisse klinische Krankheitszeichen vorlagen, die sogar bei in höherem Lebensalter stehenden Individuen die Operation als indiciert erschienen liessen, wir also mit Berechtigung annehmen dürfen, dass diese Krankheitszeichen erhebliche Beschwerden machten.

Es fand sich also die neurogene Appendicopathie im Jahre 1950 in einer *Frequenz von 7%*. Aus der gleichen Untersuchungsreihe ist zu entnehmen, dass das



ABB. 2. Obliterierte Appendix mit kleinem centralen Neurom. Orig. Präparat von R. Maresch, 1921.

weibliche *Geschlecht* mehr als doppelt so oft befallen ist, als das männliche: 23 männlichen Fällen stehen 61 weibliche gegenüber. Was die *Altersverteilung* anlangt kann gesagt werden, dass mit steigendem Alter bis gegen die Lebenswende die Frequenz zunimmt. Wir sahen unter unserem Untersuchungsgut das Maximum zwischen 40 und 50 Jahren, wobei unser jüngster Patient ein Knabe von 10 Jahren war, unsere älteste Beobachtung aber eine Frau von 74 Jahren betraf. Ob die geringere Zahl von Fällen jenseits der 50. Lebensdecade ein einwandfreies Bild liefert, müssen wir dahingestellt sein lassen, da unsere auf operative gewonnenen Appendices basierende Statistik hier unter dem Fehler leidet, dass naturgemäss die Indicationsstellung zur Operation wohl erheblich strenger gestellt wird, wenn es sich um im vorgerückten Alter stehende Kranke handelt, als bei jüngeren Individuen, bei denen das Operationsrisiko ein wesentlich geringeres ist.

Die genaue Altersverteilung in unserer Untersuchungsreihe ist aus nachstehender Tabelle zu entnehmen:

Jahrzehnt	I	II	III	IV	V	VI	VII	VIII
Zahl d. Fälle.....	1	5	10	14	25	18	8	3

Diese unsere statistischen Ergebnisse decken sich weitgehend mit jenen, welche, ebenfalls in Wien, von chirurgischer Seite, nämlich durch J. Knoflach, an seinen Fällen, die er in den auf den zweiten Weltkrieg folgenden Jahren 1945 bis 1950 operierte, erhoben worden sind. Knoflach fand unter 1492 operativ gewonnenen Wurmfortsätzen eine Frequenzhäufigkeit dieser neurogenen Appendicopathie von 10%. Demgegenüber vermerkt Anderson 1948 aus Milwaukee "it is not a common lesion." Da wir nicht den geringsten Zweifel an der Angabe Andersons, soweit sie sein Material betreffen, hegen, müssen wir annehmen, dass bei der neurogenen Appendicopathie erhebliche *geographische Unterschiede hinsichtlich der Frequenz* ihres Vorkommens bestehen. Diese bedürfen der Erklärung, um so mehr, als sich daraus vielleicht Hinweise auch auf die *Entstehungsursachen* dieses Leidens ergeben könnten.

Es mag zunächst als ein Zufall imponieren, dass sowohl Maresch, wie auch Masson, der 1921 noch in Strassburg tätig war, ihre Entdeckung dieser neurogenen Appendicopathie zur gleichen Zeit und zwar in den Jahren unmittelbar nach dem ersten Weltkrieg machten. Ebenso mag es zunächst als Zufall erscheinen, dass in dem darauffolgenden Zeitabschnitt Mitteilungen über dieses Leiden nur spärlich vorliegen. Wohl könnte man dies auch mit der vielleicht nicht ausreichenden Kenntnis dieser in den Anfangsstadien nicht ohne weiteres zu diagnostizierenden mikroskopischen Veränderungen erklären. Demgegenüber ist es aber sehr auffallend, dass Masson, wohl zweifellos der heutigentags beste Kenner der neurogenen Appendicopathie, an seinem jetzigen Wirkungsort, Montreal in Canada, wie einer persönlichen Mitteilung an Coronini zu entnehmen ist (angef. bei Lassmann), dieser neurogenen Appendicopathie nur selten begegnet ist. Diesbezüglich decken sich also die Erfahrungen Massons durchaus mit der früher citierten Aussage Andersons "it is not a common lesion."

Diese zweifellosen zeitlichen und örtlichen Unterschiede legen somit den Gedanken nahe, dass es besondere in diesen *Zeiten* und mit diesen *Orten* verbundene Momente sein müssen, welche diese Differenzen bedingen und es war naheliegend, an den wohl einschneidendsten Faktor in dieser Hinsicht, an den Krieg mit seinen so mannigfachen sowohl körperlichen, wie vor allem auch seelischen Belastungen zu denken, dessen *psycho-somatischen Auswirkungen* wohl in den Europäischen Ländern quantitativ stärker in Erscheinung treten dürften, als anderen Ortes.

Derartige bereits von vielen Seiten und für zahlreiche Leiden auch anderer Art geäußerten Vermutungen fanden in der erwähnten Publikation von Knoflach eine weitere objektive Stütze von klinischer Seite. Knoflach wies nach, dass unter seinen 95 Fällen mit neurogener Appendicopathie in der Vorgeschichte der Kranken *schwere psychische Traumen* acuter und vor allem chronischer Art 50 mal, leichtere derartige Traumen 40 mal aufschienen, die sich auch noch zur

Zeit der Operation durch den Nachweis von Tremor, Hyperhidrosis, Dermographismus und positiven Ausfall des Chvostekschen Zeichens objektivieren liessen. Nur in 5 von seinen 95 histologisch verifizierten Fällen von neurogener Appendicopathie fehlten einschlägige Angaben und Symptome! Ein hinsichtlich einer schweren psychischen Belastung freies anatomisches Vergleichsmaterial, also operative gewonnene Appendices etwa aus der Zeit vor 1914, steht uns leider nicht zur Verfügung. Wir haben versucht, die während des Jahres 1936 dem hiesigen Institute übermittelten Appendices als ein gegenüber der unmittelbaren Nachkriegszeit psychisch weniger belastetes Untersuchungsgut vergleichsweise heranzuziehen. Die Durchsicht von 1290 Appendices aus dem Jahre 1936 ergab jedoch annähernd den gleichen Hundersatz für die neurogene Appendicopathie, wie 1950. Wir können somit daraus nur den Schluss ziehen, dass anscheinend einmal gesetzte Veränderungen dieser Art lange Zeit bestehen bleiben, ja wie Feyrter meint, vermutlich überhaupt nicht mehr schwinden, aber in höherem Alter subjectiv vielleicht sich nicht mehr so bemerkbar machen, dass sie zu einer operativen Entfernung des Wurmfortsatzes Anlass geben.

Dieser Auffassung der neurogenen Appendicopathie als einer psycho-somatischen Erkrankung mag vielleicht entgegengehalten werden, dass eine sich ausschliesslich auf den Wurmfortsatz beschränkende Localisation psychischer Traumen wenig wahrscheinlich sei. Aber auch in dieser Hinsicht gibt die citierte Publikation Knoflachs interessante Aufschlüsse: Nur 64 von seinen 95 Kranken mit neurogener Appendicopathie blieben nach der Operation völlig beschwerdefrei. Bei diesen darf man also wohl mit Recht eine monotope Localisation der Veränderungen am nervösen Apparat annehmen. 15 wurden gebessert, 16 klagten weiter über abdominelle Beschwerden. In diesen letzteren Fällen darf man es als wahrscheinlich ansehen, dass die Veränderungen der geschilderten Art im Digestionstract nicht auf die Appendix allein beschränkt waren, sondern die Wucherung des nervösen Endnetzes eine weitere Ausbreitung hatte.

Als vermutlicher Sitz analoger Wucherungsvorgänge kommt schon im Hinblick auf die oft nicht leichte klinische Differential-diagnose zwischen Symptomen, die einer hochgeschlagenen Appendix und der *Gallenblase* ihre Entstehung verdanken, *letzteres Organ* in Frage. Wir haben auf die Möglichkeit einer auch anatomisch nachweisbaren "*neurogenen Cholecystopathie*" — der analoge klinische Begriff ist ja schon alt, — bereits vor Jahren hingewiesen und Kuezko hat in jüngster Zeit einprägsame Bilder dieser Veränderungen aufzeigen können, wobei auch die kleinen arteriellen Gefässe der Gallenblase gleichartiges Aussehen boten, wie die der Appendix bei neurogener Appendicopathie. Weiters konnte Obiditsch-Mayer im Wesentlichen analoge Prozesse an den Gefässen des *Dickdarms* bei mit chronischer Obstipation nachweisen, welche von Finsterer deswegen als ultima ratio hemicolectomiert worden waren. Derartige Wucherungsvorgänge am nervösen Endapparat liefern ein erwünschtes anatomisches Substrat bei bestimmten Formen von Darnleiden, deren klinisches Bild schon vor vielen Jahren O. Porges herausgearbeitet hat.

Die erwähnten Beispiele zeigen, dass Wucherungsvorgänge am vegetativen Endapparat im Bereiche des Verdauungsschlauches an zahlreichen Stellen gefun-

den werden können und zwar bei Leiden, bei denen eine nervöse Komponente heutigentags wohl allgemein angenommen wird. Sie bringen mangelhafte Erfolge der Appendectomie in Fällen von neurogener Appendicopathie dem Verständnis näher, und zeigen durch ihre Verknüpfung mit gleichsinnigen Wucherungsvorgängen des terminalen nervösen Reticulums in anderen Organen, wie wir dies nicht so selten gesehen haben, den viel weiteren Umfang des Prozesses auf. Allerdings müssen wir auf Grund unserer Erfahrungen sagen, dass die Appendix ein bevorzugter Sitz derartiger Proliferationsvorgänge am Nervengewebe ist. Ob dies mit der Eigenschaft des Wurmfortsatzes als eines rudimentären Organes zusammenhängt, oder auf andere Ursachen zurückzuführen ist, vermögen wir nicht zu entscheiden.

SUMMARY

Maresch demonstrated in 1921 that a certain number of obliterated appendices showed proliferation of nerve fibers not unlike amputation neuromas. Masson suggested a causal connection with the argentaffin cells of the mucosa which he found proliferated and displaced in this condition. While Maresch was impressed with the relief of symptoms following appendectomy in these cases the standard American texts of pathology express a reserved opinion. Some European histologists and pathologists have elaborated on this problem. Appendices without obliteration may also show proliferation of nerve fibers, frequently associated with eosinophils and increased argentaffins in the mucosa. The proliferated nerve tissue belongs to the "terminal reticulum" of Stöhr Jr. and arises from the nerve plexus of the mucosa and to a lesser extent from deeper plexus (submucous, myenteric).

Of interest is the thickening of small arteries in these appendices which is interpreted as caused by proliferation of mural nervous elements similar to that seen occasionally in von Recklinghausen's neurofibromatosis (Reubi, Feyrter, Obiditsch-Mayer). The term neurogenic appendicopathy is suggested instead of neurogenic appendicitis. Depending on the presence or absence of a lumen an open or closed form are described.

Statistical studies showed that this disorder occurred in 7% of 1249 appendices removed in 1950. The female sex being two to three times as frequently involved. The lesion is most common in the decade from 40 to 50. This frequency distribution may be fallacious because of greater restraint exercised in selecting older people for operation. A similar frequency (10%) was found by Knoflach in 1492 appendices removed between 1945 and 1950. It is conceivable that the rarity of this lesion in the United States and Canada is caused by some environmental factor. The fact that the original descriptions came from Vienna (Maresch) and Strassbourg (Masson) in the years following World War I and the fact that Masson found it only rarely in Montreal point to the possibility of a mechanism connected with the stress imposed on body and mind by the years of World War I and II. This assumption appears corroborated by Knoflach who found severe psychic traumas in 50 cases and less severe ones in 40 cases out of a total of 95.

When a control material of surgically removed appendices from a relatively quiet year (1936) was examined the percentage was about the same. This does not necessarily negate the hypothesis offered before but is taken as evidence for the irreversibility of the structural alteration. Of Knoflach's 95 cases 64 only were cured permanently. The failures may very well be due to spreading of the proliferative process of the nervous terminal reticulum to other hollow viscera. Indeed analogous morphological changes have been demonstrated in the gall-bladder (Kuesko) and colon (Obiditsch-Mayer). The colonic lesions were found in patients with severe chronic constipation.

Thus it is evident that proliferative changes of the nervous terminal reticulum are not too uncommon in the alimentary canal and may possibly be a substrate of various clinical states.

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ÜBER AUTOMATIK UND DEREN GRENZEN

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Nahezu alles Geschehen im Kosmos erfolgt automatisch. Nur in verschwindendem Masse vermag der Mensch in diese Zwangsläufigkeit einzugreifen und sich diese dadurch dienstbar zu machen. Ja, es kann fraglich sein, ob nicht auch dieses Eingreifen zum Teile oder zur Gänze durch ihn automatisch und unabhängig von einem freien Willen erfolgt.

Durch die Sinnesorgane vermochten Beobachtung und Forschung eine ungeheure Fülle automatischer Abläufe zu erfassen, aber das, was dabei zu unserer Kenntnis gelangt ist, ist nur *Erscheinung*, ohne dass es möglich wäre, in irgend einem Belange bis in das Grundwesen dieser Erscheinungen einzudringen und die Kausalität des *Seins* zu erfassen.

Erscheinungen, die nach unserer Sinneswahrnehmung immer in der selben Art erfahrungsgemäss abzulaufen pflegen, werden auf Grund statistisch festzustellender Wahrscheinlichkeit in der Form von Gesetzen zusammengefasst. Es kann aber kein Zweifel darüber bestehen, dass kein einziges Gesetz mehr als der Ausdruck einer gewissen Wahrscheinlichkeit ist, und dass kein einziges Geschehen in belebter und lebloser Natur bis in sein Grundwesen voll erklärt werden kann.

Kraft, elektromagnetische Schwingung, Gravitation erkennen wir nur aus Wirkungen und durch sie mögliche Veränderungen, die sinnlich mittelbar oder unmittelbar wahrnehmbar sind, und deren Wahrnehmbarkeit eben durch die Leistungsfähigkeit unserer Sinnesorgane, einschliesslich ihrer Fehlurteile, begrenzt ist. Was nicht irgend wie und irgend wann jemals sinnlich erkannt werden konnte, besteht für uns nicht. Von einer Billion von Schwingungen, die auf unseren Körper auftreffen, kommt vielleicht im Durchschnitt nur eine einzige zu unserer Wahrnehmung, wenn es auch gelingt, durch entsprechende Umformung, eine Fülle von Strahlenarten, welche die Sinne nicht unmittelbar zu verwerten vermögen, der objektiven Erfassung durch unsere Sinne zugänglich zu machen.

Auf dem, was unsere Sinnesorgane wahrzunehmen gestatten, baut unsere *Sinneswelt* auf. Der menschliche Geist verknüpft die Sinneseindrücke durch sein Kausalitätsbedürfnis zu seiner *Verstandeswelt* und über dieser baut sich noch sein *hypothetisches Weltgebäude* auf, das über die Verstandeswelt hinauszukommen strebt und durch die Sinneswelt begrenzt ist, da eine Hypothese nur in so lange bestehen kann, als sie nicht mit kontrollierbaren Aussagen der Sinneswelt in Widerspruch gerät.

Jeder Sinneswahrnehmung liegt ein automatisches Geschehen zugrunde. Jede Sinneswahrnehmung ist bedingt durch das Auftreffen von Wirkungsquanten, die chemische und physikalische Veränderungen nach Art einer Kettenreaktion auslösen. Aber jedes Wirkungsquant, jede Welle, jedes Elektron, Proton oder Meson ist schon an und für sich ein Automat. Jede Umformung einer Energie,

sei es nun das Auftreffen eines Protons und dessen Umwandlung in Wärme, Bewegung, farbiges Licht, elektrischen Strom oder was immer, ist Automatik. Was die Ursache solcher Automatik ist, wissen wir so wenig, wie wir wissen, was ein Atom ist, dem jedes Charakteristikum von Substanz fehlt, oder was Kraft oder Schwingung, nach ihrem *Sein* gefragt, in Wirklichkeit sind.

Atome bergen in sich automatische intraatomare Kräfte; sie ketten sich durch interatomare Kräfte zu Molekülen zusammen und diese gehen Reaktionen unter automatischem Austausch von Elektronen an den äussersten Elektronenschalen als Verbindungen ein, in Lösungen dissoziieren die Moleküle automatisch und es folgt dann die Summe der dissoziierten Ionen und nicht dissoziierten Moleküle, dem Gasgrundgesetz. Warum? Dies ist ebensowenig zu beantworten, wie es eine Antwort darauf gibt, warum Elektronen um die Atomkerne kreisen, warum die einen in näheren, die anderen in entfernteren Bahnen liegen, oder warum es überhaupt Protonen, Elektronen, Neutronen und Isotope gäbe. Moleküle bauen sich durch Polymerisation auf zu Grossmolekülen und Riesenmolekülen von mehreren Millionen Molekulargewicht. Moleküle verketten sich automatisch zu Körpern in zwangsläufigen Formen von Kristallgittern, Bändern, Spiralen, Kugeln oder walzenförmigen Gebilden und diese werden in mannigfaltigster Art zusammengefügt zu Substanzen, Organen und Lebewesen, angefangen von den kleinsten Formen bis zu den Giganten einer Sequoia oder eines Riesensauriers. In der leblosen Welt bilden sie die molekulardispersen, kolloid-dispersen und grobdispersen Phasen bis zu körperlichen Massen, von kosmischem Staub, bis zu Planeten, Sonnen, Galaktonen und Kugelhaufen. Automatisch erfolgt die Bewegung der Himmelskörper wie jene der Elektronen um die Kerne; automatisch fliehen die entferntesten Himmelskörper mit 40.000, vielleicht 60.000 km. pro Sekunde von unserem Sonnensystem weg und weiten das Weltall. Zwangsläufig entsendet die Sonne ihre, aus der Umformung von Wasserstoff, in Helium erübrigte Energie auf unsere Erde, und diese hält seit etwa 1000 Jahrmillionen ihre Oberflächentemperatur in stetem Ausgleich zwischen Zustrahlung, Abstrahlung und Erzeugung innerer Wärme durch atomare Prozesse auf annähernd gleichmässiger Temperatur, die nur etwas in automatisch wechselnden Wärme- und Kälteperioden, Perioden hochgradiger vulkanischer Tätigkeit und grösserer Ruhe, schwankt. Automatisch wechseln Tages- und Jahreszeiten, verschieben sich Kontinente, wachsen und senken sich Gebirge und werden durch Erosion abgetragen. Automatisch verläuft der Kreislauf der Elemente. Zwangsläufig folgen einander Werden, Sein und Vergehen. Und ebenso automatisch entstanden zuerst Wassertiere, dann Wasserpflanzen, folgte dem äusseren Panzerskelett das Knorpel- und Knochenskelett. Neue Tier- und Pflanzenfamilien traten auf, andere verschwanden. Auch im Weltall vollzieht sich Werden, Sein und Vergehen. Der Mensch beobachtet all dies Geschehen in *der* Art, wie ihm dies seine Sinnesorgane ermöglichen und das, was er subjektivistisch zu erkennen vermeint, extrapoliert er auf das Geschehen in der Gesamtwelt und auf das Verhalten von anderen Lebewesen, ohne eine Ahnung davon zu haben, wie sich all die Automaten auf diese, z.B. die Tiere, die doch zum Teil ganz andere Sinnesorgane haben, zum Teil Sinnesorgane, die den unseren

weit überlegen sind, auswirkt. Haben wir doch keine Ahnung wie ein Frosch oder ein Insekt die Welt sieht und wahrnimmt. Hilflos steht der Mensch all dem *Sein* gegenüber, in das er nur, eng begrenzt durch seine Sinne, subjektiv, Einblick zu nehmen vermag.

An *vier Cäsuren* versagt derzeit jeder Versuch kausaler Erklärung der Erscheinungen und der diesen innewohnenden Automatik.

Die *erste Cäsur* liegt im Versagen jeder Kausalität an der Grenze des Kleinsten wie dies durch Heisenbergs Unbestimmbarkeits-Relation gekennzeichnet ist.

Die *zweite Cäsur* ist gegeben durch die Begrenzung der Gültigkeit der statistisch unzweifelhaft feststehenden und fundamentalen beiden Hauptsätze der Thermodynamik. Ist schon der zweite Hauptsatz nur in begrenztem Masse auf die Vorgänge im Lebenden anwendbar, so versagt auch der erste Hauptsatz bei der Frage: Woher kam das ungeheure Potential, die ungeheure Summe möglicher freier Energie des Weltalls; woher kam die Automatik, die alle Energie beherrscht und diese in zwangsläufige Gesetze zwingt, wie sie jeder einzelnen Energieform innewohnen und jeder Umwandlung einer Energieform in eine andere, der Umwandlung von Kraft in Stoffe und jener von Stoff in Kraft zugrunde liegt. Wissen wir, ob der Kosmos tatsächlich dem Ausgleich aller Potentiale, der Vernichtung jeder freien Energie und damit dem wahrscheinlichen Zustand energieloser allgemeiner Unordnung zustrebt und ob nicht der Vernichtung der Potentiale automatisch oder durch Schöpfungswillen ein Neuaufbau des Weltpotentials erfolgt und der gegenwärtigen Welt, wie dies schon Heraklit annahm, immer wieder automatisch eine neue Welt folgt.

Über die zweite Cäsur vermag nur die Einführung transzendenter Vorstellungen hinwegzuführen. Woher kam die Kraft, woher der Raum? Wie kann ein Raum zu einem Nichtraum werden, kann doch ein Raum nur durch eine Begrenzung charakterisiert werden und jede Begrenzung hat zur Voraussetzung, dass etwas Begrenzendes da sei. Dies könnte nur eine Kraft oder ein Stoff sein. Trennte nun der Schöpfer von seinem Raum ab, gab er von seinem Kraftvorrat ab, so schuf er damit die Zeit und es fragt sich, was tat der Schöpfer vor dieser Zeit und seit wann lief diese, seine Zeit? Wurde der Schöpfer durch die Schaffung des Kosmos ärmer an Kraft und Raum?

Doch um Kraft und Raum zu schaffen oder Kraft in den Raum zu entsenden, bedurfte es eines Willens. Dieser Wille musste aber selbst eine Kraft sein, um Kräfte steuern zu können und durch diesen Willen musste erst die Automatik in die Kraft und das Geschehen in den Kosmos gelegt werden. Man kann kaum annehmen, dass der Schöpfer durch die Schöpfung, die nur überautomatisch sein kann, weniger geworden sei. Sollte der Kosmos nur ein vollkommen automatisches Werk sein? Dies führt zwangsläufig zur unvorstellbaren Vorstellung der Unendlichkeit. Können wir uns doch etwas Unendliches—sei es in Form einer Acht oder in der eines Kreisumfanges—trotz deren Endlosigkeit, nur endlich vorstellen. Es kann die Automatik nur auf einer Unendlichkeit des Schöpferwillens, der sich nicht verbrauchen oder mindern kann, beruhen, eines Willens, der nicht der Zeit unterworfen, immer auch entgegen den scheinbar ehernen Gesetzen wirken kann.

Die *dritte Cäsar* liegt zwischen der Automatik des Leblosen und des Lebenden. Formänderung, Stoffänderung und Kraftänderung laufen automatisch auch im Leblosen ab. Im Lebenden finden sich keine anderen Atome als wie im Leblosen; deren Automatik liegt daher auch allem Geschehen im Lebenden zugrunde. Insofern ist jedes Lebende Automat. Und doch treten im Lebenden sprunghaft neue Automaten auf, die es im Leblosen nicht gibt. Alle Versuche, deren Zustandekommen kausal erklären zu wollen, haben versagt. Auch die Zufallshypothese ist vollkommen unhaltbar.

Wie soll ein Eiweissmolekül, das stickstoffhaltig ist und ein Molekulargewicht von 20.000 hat, zustande kommen? Solche Moleküle—geschweige denn Virusmoleküle von 5 Millionen Molekulargewicht und mehr—gibt es im Leblosen nicht. Es ist schon unfassbar wie aus den 10^{79} Ionen im Weltall durch zufälliges Zusammentreffen von Atomen ein Molekül vom Bau eines Eiweissmoleküls entstehen sollte, und es wird das Mass der Unwahrscheinlichkeit schon verständlich, selbst wenn man annimmt, dass ein bestimmtes Eiweissmolekül nur aus zweierlei Atomen aufgebaut wäre und nur 20.000 Moleküle enthalten würde. Es würde dann der Zufall, dass ein solches zustande käme, nur einer Wahrscheinlichkeit von $1:2,02^{321}$ entsprechen. Zu unfassbarer Grösse steigt aber diese Unwahrscheinlichkeit, wenn man an die Grösse eines Virusmoleküls denkt, das den Übergang vom Leblosen zum Lebenden vorstellen soll und bedenkt, dass dies nicht nur zweierlei Atome, sondern ausser Stickstoff und Kohlenstoff noch Sauerstoff, Schwefel, Eisen und Phosphor enthält, zudem Kalium und Natrium und dass in einem solchen Molekül jedenfalls mehr als 100.000 Atome vorhanden sind. Mit Recht sagt *Eddington*, dass ein Mensch, der sich über eine solche Unwahrscheinlichkeit hinwegsetzen wollte, ein überaus interessantes, statistisch zu erfassendes Seltenheitsexemplar sein müsste. Aber selbst dann, wenn wirklich einmal ein solches Virusmolekül entstanden sein sollte, so würde dies ja noch immer leblos sein und erst die Frage entstehen, wie dies zur Automatie des Lebenden erweckt wurde oder wie ein zweites solches Virusexemplar, für das sich das Zustandekommen schon gar nicht mehr wahrscheinlichkeits-statistisch ausdenken liesse, das Leben bekommen habe, um es auf das erste Virusmolekül zu übertragen. Teilung, Vermehrung, Vererbung, Mutationsfähigkeit, dadurch die Fähigkeit zu weiterer Fortentwicklung unter höherer Differenzierung, die Fähigkeit zu Assimilation und Dissimilation, zu Kraft- und Stoffwechsel, wäre damit immer noch nicht gegeben. Mit einer Automatik des Werdens von Lebendem aus Leblosem zu rechnen, steht somit wohl, nach derzeitigen Vorstellungen, ausserhalb jeder Möglichkeit.

Man kann sich der Annahme nicht entziehen, dass das Leben, das auf das leblose Virusmolekül übertragen wird, und das nur von Lebendem stammen kann, auf irgend welcher Energie beruhen müsse. Bemerkenswert ist es jedenfalls, dass für den Eintritt einer Lebensautomatik, das Vorhandensein von Phosphor, speziell der Thymonukleinsäure, erforderlich ist. Sie findet sich im Virusatom diffus und wird in den Acytariern schon in Stränge eingebaut, um dann in den Cytariern in Form der Chromatin-Schleifen des Zellkerns aufzutreten. Phosphor findet sich überall, wo Teilung und Vermehrung stattfindet, überall,

wo eine Bewegung erfolgt; in Geissel- und Flimmerzellen, in allen Muskeln, aber auch im Gehirn und peripheren Nervensystem. Phosphorverbindungen sind bei jeder Umsetzung bei der Muskelkontraktion erforderlich. Es scheint somit, dass das Phosphoratom irgendwie zwangsläufig mit den Lebensprozessen zusammenhängt.

Ein automatisches Verhalten bei der phylogenetischen Entwicklung der Tier- und Pflanzenwelt, ist einem kausalen Verständnis viel leichter nahezubringen. Obwohl es dabei der Potentialsprünge noch genug gibt, ist es denkbar, dass es möglich sein kann, sich mit diesen durch neue Funde von Übergangsstufen abzufinden. Spontanmutationen, Mutationen durch Umweltfaktoren bedingt, der Ausfall von Tierarten, die den Umweltfaktoren nicht angepasst waren, oder sich den neuen Umweltfaktoren nicht anzupassen vermochten, das Aussterben von abwegigen Formen, ebenso die Unfruchtbarkeit und die fehlende Vererbung bei Minusvarianten, polyploiden Formen und Missbildungen, lässt es immerhin möglich erscheinen, dass durch das Auftreffen von Wirkungsquanten—wie dies die Drosophilaversuche klar erwiesen haben—mit einer Wahrscheinlichkeit. Die der Trefferwahrscheinlichkeit entspricht, fortschreitend neue Formen entstanden sind, die zu einer zielstrebig aufwärts drängenden Differenzierung in somatischer und funktioneller Beziehung geführt haben, so dass neue Arten, Gattungen und Familien entstehen konnten, in denen sich immer mehr und kompliziertere Automaten ausbilden konnten. Diese Automaten wurden dann zugleich automatisch untereinander zusammengefasst, um der Erhaltung des Lebens zu dienen und die Leistungsfähigkeit der Individuen sicherzustellen, sie gegen die Umweltfaktoren zu schützen oder deren Ausnutzung zu ermöglichen. Man pflegt die automatische Verknüpfung von Automaten mit dem Worte *Korrelationen* zu bezeichnen. Alles Forschen geht dahin, solche Korrelationen aufzudecken und in erkennbare Automaten zu zerlegen. Da dies aber nur insoweit möglich ist, als es der Fortschritt experimenteller Technik gestattet, die Vorgänge sinnlich zu erfassen, muss jede Fragestellung, jede Forschung und Forschungsmethodik zeitbedingt, gewissermassen modenhaft bleiben, bis nicht neue Wege zum Eindringen in ein Geschehen auf dem Wege unserer Sinne geschaffen sind.

Humorale und nervöse, chemische und physikalische Automaten sind in einer Unsumme von verwickelten Korrelationen zu Steuerungen zusammengefasst, die zu der Einhaltung einer bestimmten Wasserstoff-Ionenkonzentration, zur Regelung des Ionenmilieus, der Lösungs- und Quellungsvorgänge, und zur Regelung des Stoff- und Kraftwechsels führen, sowie eine bestimmte, für das betreffende Lebewesen erforderliche Temperatur für den Warmblüter gewährleisten, um diesem die zureichende Reaktionsgeschwindigkeit für die trophotropen und ergotropen Leistungen zu sichern und damit die Erhaltung des Lebens zu gewährleisten. Angeborene und erworbene Reflexe, chemisch-physikalische Reizungen und Veränderungen der Reizbarkeitslage wirken zusammen, in die der Mensch u. a. regelnd durch pharmakologische Mittel einzugreifen bestrebt ist.

Zu den Meistern, denen die medizinische Wissenschaft wesentliche Fortschritte in dem Einblick in solche automatische Korrelationen humoraler und

nervöser Steuerung verdankt, zählt die Schule H. H. Meyers und in ihr nennen wir mit Stolz E. P. *Pick*, O. *Loewi* und A. *Fröhlich*.

E. P. *Pick* war es, der der Lehre von den sympathikotropen und vagotropen Pharmaka, jener von kortikal und subkortikal angreifenden Pharmaka, neue fruchtbare Wege gewiesen hat, und durch die Entdeckung der Lebervenensperre einen vollkommen neuen Gesichtspunkt in die Kreislaufsphysiologie gebracht hat. Er war es, der in den Enden des His'schen Bündels ein eigenes automatisches Zentrum dritter Ordnung erkannte.

O. *Loewi* hat, durch die Entdeckung des vagotropen- und sympathikotropen Herzhormons für die Lehre der automatischen humoralen Steuerung der Herzarbeit, der Physiologie und Pathologie vollkommen neue Wege gewiesen. Wie wundervoll ist doch die automatische Korrelation der Steuerung der Vorgänge in Kreislauf und Atmung. Im Herzen wirken, hintereinander geschaltet, drei automatische Zentren, neben diesen bestehen receptorische Nervenendigungen, die auf die Dehnung der Herzmuskelfasern eingestellt sind, und den *Jarisch* Reflex bedingen, der die Füllung des Herzens regelt; an der Mündung der Hohlvenen liegen receptorische Elemente, die auf Dehnung der Mündungsgegend eingestellt sind. Am Anfangsteil der Coronarien sind Steuerungsmechanismen eingebaut, die humoral und auf Druck eingestellt sind; sie helfen die Arbeit des Herzens, durch Änderung der Durchblutung der arteria crista terminalis, steuern. Pressorreceptoren liegen am Anfangsteil der Aorta und im Sinus Caroticus. Vagus und Sympathicus wirken als Zügler des Herzens, im Zusammenspiel mit den sympathischen und parasympathischen Zentren des Rückenmarkes. Darüber stehen die Zentren der Medulla oblongata, die automatisch, humoral und nervös reflektorisch gesteuert werden. Durch *Hess* wurde dann die übergeordnete zusammenfassende Rolle des Zwischenhirns und jene eines sekundären Zentrums für Blutdruck-Regulierung im Stirnhirn erkannt, auf das von vielen Teilen der Grosshirnrinde ausgehende Einflüsse übergeschaltet werden. Zusammengefasst regeln all diese Einrichtungen gemeinsam mit hormonalen Stoffen die Funktionen aller Organe, Aufsaugung, Ausscheidung, Muskelarbeit, Körpertemperatur, Fortpflanzung, Wachstum und Regeneration bis an das Lebensende, das mit einem Stillstand aller Regulationen und Automaten nach längerer oder kürzerer Zeit verknüpft ist. Worin aber das Lebensende besteht, wodurch der Ausfall der Lebens-Automatik erfolgt, ist ebenso unbekannt, wie der Ursprung derselben. Kein einziges physikalisches oder chemisches Geschehen deutet darauf hin, welche Energie oder welcher Stoff verschwunden ist, der für den Antrieb zu all der Automatik verantwortlich war. Wie das Leben verlief, so endet es auch automatisch.

Die *vierte Cäsar* schien vor etwa 100 Jahren, in jener Zeit, von der Gottfried Keller in seinem Sinngedicht sagt, "als die Naturwissenschaften wieder einmal ihre höchste Höhe erreicht hatten", leicht zu überwinden. Es war fast eine Selbstverständlichkeit, dass der Mensch von den anthropoiden Affen abstamme, und sich automatisch aus diesen weiter entwickelt habe. So sehr es offenkundig zu sein scheint, dass der Mensch eines der gegenwärtig lebenden Endglieder zielstrebigster phylogenetischer Entwicklung ist, so sicher ist es, dass der Mensch

nicht von den anthropoiden Affen abstammt. Es ist — wegen deren geringen Zahl — höchst unwahrscheinlich, dass Funde von Resten der ersten Urmenschen gemacht werden dürften, und beinahe ebenso unwahrscheinlich ist es, dass Knochenreste von diesen die Jahrzehntausende, ohne durch Verwitterung zugrunde zu gehen, überstanden haben. Jedenfalls stammen jene Funde von Urmenschen, die bisher gemacht wurden, und auf Grund gleichzeitiger Funde von Kulturleistungen als Menschenfunde gekennzeichnet waren, von Vollmenschen gewesen und keine affenartigen Tiere oder Übergangsformen zu diesen vorstellen, wie es ebensowenig heute noch überlebende primitivste Volksreste sind. Keineswegs war, nach der Grösse des Schädelinehaltes zu erweisen, dass eine progressive Cerebration innerhalb menschlicher Rassen stattgefunden habe. Auch die Frage, wann der Mensch die Sprache erwerben konnte, die auf Grund seines Unterkieferbaues erst ermöglicht worden sein soll, ist überaus strittig. Anscheinend hat der Urmensch ebenso die Fähigkeit zu sprechen besessen, wie der Mensch der Gegenwart, und ebenso muss er bereits das Feuer verwendet haben, das jedes Tier scheut. Wenn ein Papagei sprechen kann, so wäre es unverständlich, warum es gerade dem Menschen eine relativ bescheidene Rückständigkeit des Unterkiefers unmöglich gemacht haben sollte, Sprachlaute hervorzubringen, wogegen es gewiss nicht minder auffallend erscheint, dass es noch nie gelungen ist, trotz aller möglichen Dressurversuche, einen Affen zur Aussprache eines einzigen Wortes zu bringen. Ist schon die vierte Cäsur, somatisch zum mindesten, derzeit nicht zu klären, so gilt dasselbe auch von den psychischen Leistungen. Gewiss bestehen in vielen Belangen gewisse Ähnlichkeiten zwischen dem Verhalten höherer Tiere und jenem des Menschen und sicherlich ist vieles, was bei Tieren als Instinkt oder bedingter Reflex aufgefasst wird, dasselbe, was beim Menschen als psychische Leistung angesehen wird, und ebenso sicher ist vieles, was beim Menschen transzendent, psychisch zu sein scheint, nichts als Automatik, und doch ist auch darin der Abstand unüberbrückbar. Das höhere Tiere hat ein Erinnerungsvermögen, ein Gedächtnis, ja, sogar bis zu einem gewissen Grade, freien Willen. Ein Hund weiss, dass er nicht stehlen soll, er zögert und überlegt, ob er dem instinktiven Trieb folgen soll oder ob ihn ein bedingter, anerzogener Reflex davon abhalten soll, und stiehlt er doch, so zeigt er ausgesprochenes Schuldbewusstsein und weiss, dass er in der Wahl gefehlt hat. Auch Tiere haben Affekte, zeigen Freude, Trauer, Hass, Feindschaft, Freundschaft, sind nachtragend oder bösartig, sie kennen Unterordnung unter einen Führer, vereinigen sich zu Gemeinschaften, um sich gegenseitig zu unterstützen. Gewiss kann man es nicht als angeborenen Instinkt oder als anerzogenen Reflex auffassen, wenn Pelikane einen blinden Artgenossen fürsorglich mit Fischen füttern wie ein hilfreicher Mensch. Es scheint sicher zu sein, dass Hunde träumen. Sie laufen und bellen im Schlaf, wie es Menschen gibt, die träumend sprechen oder pfeifen. Wieviele beim Menschen ist automatisch, ja, automatisch entgegen intensivstem Wollen. Vergeblich trachtet ein Mensch, eine Lösung zu finden, oder sich an irgend etwas zu erinnern. Im Schlafe, auf einem Spaziergang, beim Billiardspiel (Mozart), ja, sogar beim Auftauchen nach einem Kopfsprung (Berlioz), ist auf einmal eine Lösung, ein gesuchtes

Thema oder eine Melodie da. Andererseits bemühen wir uns vergeblich, den Gedanken, das Haustor nicht versperrt zu haben, das Licht nicht abgedreht zu haben oder eine Melodie, die uns geradezu quält, im Laufe eines Tages los zu werden. Den Verbrecher verfolgt die Erinnerung an seine Tat, der Süchtige will nicht, der Trinker, der Masturbant, der Jähzornige will mit aller Macht gegen sich ankämpfen und doch kann er nicht. Unmöglich ist es, gewollt zu träumen, aber automatisch stellen sich logische Gedankenfolgen ein. Und wievielen ist in den Handlungen des Menschen automatisiert, wievielen erfolgt automatisch, was man, gewollt, gar nicht könnte und doch gehört auch zur Auslösung vieler solcher Automaten ein Wille; auch dann, wenn dieser nicht freier Wille ist.

Es ist sicher ganz unmöglich allgemein zu sagen, wo das Automatische bei dem, was uns psychisch zu sein scheint, endet und wo wir auf rein transzendente Vorgänge schliessen müssen. Gibt es vielleicht nicht doch eine Möglichkeit für, eine hypothetische Erklärung psychischer Vorgänge auf Grund physikalisch-chemischer Vorgänge? Die Tatsache, dass durch die elektrische Reizung des Zwischenhirns, wie sie *Hess* ausführte, "psychische Äusserungen" bei der Katze erzielt werden können, die sich als Affekt, Bösartigkeit, Freude, Schläfrigkeit u.a. ausdrücken, die Tatsache, dass durch die Abtrennung des Stirnhirns, psychische Störungen behoben werden können, andererseits durch bestimmte kortikale Läsionen Geschwätzigkeit, Leichtsinn, Vergesslichkeit und moralische Defekte ausgelöst werden können, ja, dass beim Paralytiker unter nachweislichen pathologischen Veränderungen im Gehirn schwere psychische Störungen auftreten, all das deutet darauf hin, dass den psychischen Vorgängen morphologische und chemisch-physikalisch bedingte Elemente zugrunde liegen müssen, die darin begründet sind, dass Wirkungsquanten, die über die Sinnesorgane chemisch-physikalische Zustandsänderungen im Gehirn herbeiführen, nunmehr zu geänderten Reaktionen Anlass geben. Sicher sind uns heute Energieformen ebenso wenig bekannt, wie uns vor 100 Jahren nichts von Röntgenstrahlen, von Radiumemanation, von Atomenergie oder kosmischer Strahlung bekannt war. Versucht man nun anzunehmen, dass es so wie Gravitation und elektromagnetische Energie, auch eine ubiquitäre psychische Energie im Weltall gibt, und nimmt man an, dass diese nur dann Erscheinungen auslöst—jene Erscheinungen, die wir als psychisch bezeichnen—wenn hierfür entsprechende Empfänger vorhanden sind, so ist es verständlich, warum ein Stein oder ein Stück Eisen keine psychischen Erscheinungen zeigen kann, dass aber solche bereits bei niedersten Tieren vorkommen können, weil in ihnen bereits die ersten Anfänge der Ausbildung von Empfängern für die psychischen Impulse gegeben ist. Phylogenetisch entwickelt sich dann nicht die Zellseele zur Pflanzen—Tier—und Menschen—Seele, sondern es entwickeln sich nur in immer weiterer Differenzierung die Empfänger für psychische Energie. Im Genom und in den chemischen Genen überträgt sich die Anlage zu diesen Empfängern je nach der Zell—und Tierart und entwickelt sich in jedem Lebewesen mit zunehmendem Alter. So wäre die Frage, wann das Kind seine seelischen Eigenschaften bekommt, illusorisch, denn es bekommt der menschlichen Anlage gemäss in den Chromosomen die

Anlage zur Ausbildung der Antennen für die Seelenenergie mit. Demnach könnte es auch keine gute und keine schlechte Seelenenergie geben, wie es keine gute und schlechte Gravitation gibt, und demnach würde auch die Seelenenergie unvergänglich sein und nur der Empfänger mit seinen Antennen sterben. In einer solchen Vorstellung liegt keineswegs die Auslieferung des Menschen an einen hoffnungslosen Fatalismus oder ein Absprechen jeder Verantwortlichkeit. Denn nur ein Teil des Genoms ist dominant vererblich und unabweislich gegeben—wie beim schwer Belasteten—und dieser ist für seine Missetaten auch nicht verantwortlich. Der andere Teil des Genoms ist plastisch, durch Umwelt und Erziehung beeinflussbar und ausserdem sind durch Erziehung, also durch Sinnesindrücke, Hemmungen und Bahnungen für den Ablauf von Reaktionen weitgehend ausbildbar, sowohl als Ursache für bedingte Reflexe, als auch als Auswirkung einer Änderung des physikalisch-chemischen Substrates mit dem Erfolge geänderter Reaktionsbereitschaft. Impulse über die Sinnesorgane dürften Engramme in Form stereochemischer Umlagerungen in die Zellen des Gehirns setzen und damit wird auch gewiss eine Verschiedenheit im Ansprechen auf äussere Reize bedingt. Es wäre möglich, dadurch die Zwangsläufigkeit gewisser ungewollter Denkvorgänge dem Verständnis näher zu bringen. Und doch vermögen alle derartigen Hypothesen nicht, über die Notwendigkeit geistige Leistungen des Menschen auf transzendente Ursachen zurückzuführen, ganz hinwegzuhelfen. Die Vorstellung des Ich, die jederzeit spontan erweckt und überdacht werden kann, ist ohne jeden äusseren Anlass durch freien Willen möglich, und niemals durch Automatik zu erklären, auch wenn man eine psychische Energie annehmen wollte; ebensowenig können die Höchstleistungen von Kunst und Wissenschaft in ihrem willkürlichen Entstehen als voll-automatische Erscheinungen erklärt werden. Der Versuch, den Menschen als Vollautomaten zu betrachten, gelingt unweigerlich nur bis zu einer Grenze, an der jeder Versuch einer physikalisch-chemischen Erklärung versagt. Auch durch die Annahme psychischer Energie ist eine Überwindung der vierten Cäsur nicht möglich. Gewiss hat das Tier Empfänger, die aber nicht zur Gänze jenen des Menschen entsprechen, und darum wird kein Tier jemals zu menschlichen Leistungen befähigt sein. Aber auch des Menschen psychische Leistungen sind allein durch noch so geeignete Empfangsapparate nicht zu erklären. Je tiefer der Gedanke versucht, in den Urgrund des Geschehens im Kosmos einzudringen, umso sicherer tritt ihm die Erkenntnis der Begrenztheit der Erkenntnis des *Seins* und *Wollens* vor Augen und umso grösser wird die Bewunderung und das Staunen über das Unerfassbare der Unendlichkeit, die im Werden und Sein, von Kraft, Stoff und Automatie im Transzendentalen wirkte und wirkt.

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GEWÖHNUNGSVERSUCHE AN FIBROBLASTENKULTUREN*

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Die Zahl der analgetisch wirksamen Substanzen vergrößert sich ständig. Damit wächst für den Pharmakologen die Dringlichkeit, solche Verbindungen auf suchterzeugende Eigenschaften zu prüfen. Bisher fehlt es jedoch an einfachen und zuverlässigen Testmethoden.

Mit Opiumalkaloiden haben japanische Autoren (2) Gewöhnung und "Sucht" auch an Gewebekulturen *in vitro* zu demonstrieren gesucht. Als Zeichen der Süchtigkeit deuteten sie eine nach vorheriger Gewöhnung eintretende Wachstumsabnahme, wenn das Alkaloid plötzlich entzogen wurde. Das gelang am leichtesten mit Eukodal, Morphin und Heroin, schlechter mit Codein und Dionin und nur unvollkommen mit Papaverin.

Die Ergebnisse dieser Arbeiten haben wir in einer Versuchsreihe mit Morphin nachgeprüft; überdies liessen wir die synthetischen suchterzeugenden Stoffe "Dolantin" (Demerol) und "Polamidon" (Amidone, Methadone) auf Gewebekulturen einwirken und untersuchten, ob sie sich daran gewöhnen lassen und beim plötzlichen Entzug Abstinenzerscheinungen aufweisen.

METHODIK

Kulturen von Fibroblasten aus den Beinen 8-9 tägiger Hühnerembryonen wurden mit der üblichen Objektträgermethode im hängenden Tropfen gezüchtet. Nach 10 Passagen, also an Reinkulturen von Fibroblasten wurden die Versuche begonnen. Das Nährmedium bestand aus dem wässrigen Extrakt 8-9 tägiger Hühnerembryonen, dem Plasma junger Hühner und Ringerlösung im Verhältnis 3:2:1. Bei den Versuchskulturen enthielt die Ringerlösung das Pharmakon. Die Kulturen wurden im Brutschrank bei 38° C gehalten und alle 48 Stunden umgesetzt.

Die Beobachtungsreihen bestanden im Allgemeinen aus 15-20 Einzelkulturen. Hiervon wurde die aus den grösseren Einzelkulturen bestehende Hälfte zur Auswertung herangezogen und dadurch die durch technische Mängel verursachten Fehler möglichst klein gehalten.

Das Wachstum wurde mit einem Planimeter gemessen, nachdem die Umrisse vorher auf eine Mattscheibe projiziert und abgepaust waren. In den Kurven ist das Verhältnis des absoluten Wachstums der vergifteten Kulturen zu den unter gleichen Bedingungen gehaltenen Kontrollkulturen aufgetragen. Das absolute Wachstum der Kontrollen schwankte zwischen 2580-4050 m/m² mit einer durchschnittlichen Abweichung von $\pm 9\%$.

Morphin wurde in Form seines salzsauren Salzes verwendet, Dolantin und Polamidon aus den handelsüblichen Ampullen.

BESCHREIBUNG DER VERSUCHE

A.) *Morphin*: (Abbildung 1). Ein Zusatz von 1/10,000 Mol beeinflusste das Wachstum der Kulturen im Verhältnis zu den Kontrollen nicht. Dagegen sah man bei mikroskopischer Betrachtung in den meisten vergifteten Kulturen winzige Vakuolen bei gut erhaltener Zellform. Schon in der zweiten Passage waren

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diese Vakuolen verschwanden, trotzdem die Morphinkonzentration beibehalten wurde. Daraufhin wurde die Dosis auf 1/5000 erhöht. Tut man das nicht, soll nehmen das Wachstum allmählich abnehmen; eine Erscheinung, die von den früheren Untersuchern als Symptom relativen Morphinmangels gedeutet wurde. Die Konzentrationserhöhung wirkte sich zunächst nicht auf die nach 48 Std. erreichte Grösse aus. Aber die nun schon stärkere Schädigung konnte an der reichlicheren Verfettung, der vakuoligen Degeneration und der plumpen und breiten Zellform der Fibroblasten erkannt werden. Deutliche Anpassungs-

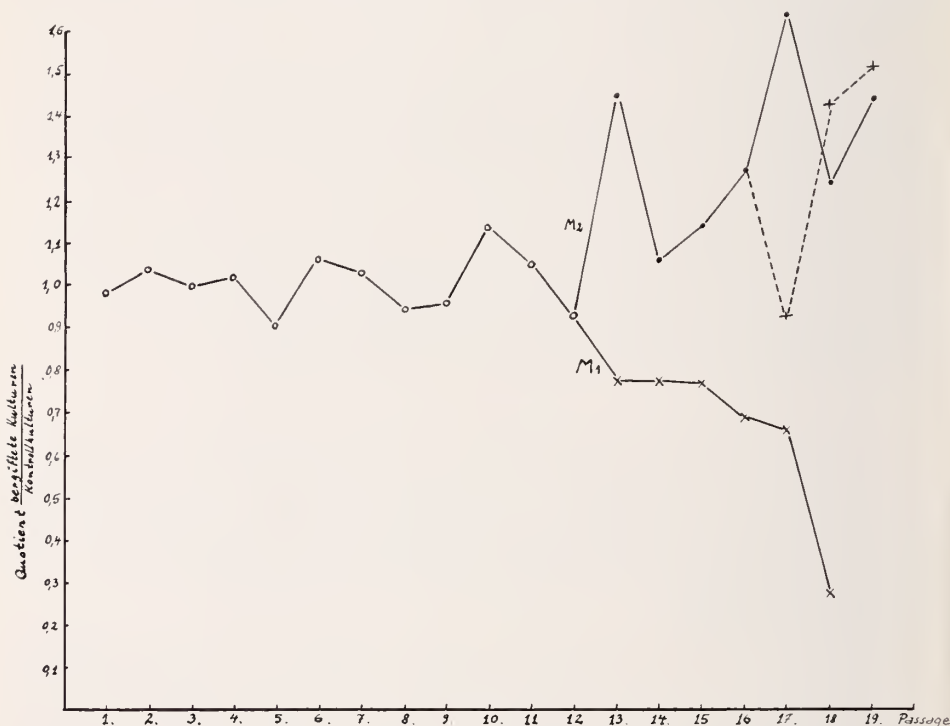


ABBILDUNG 1: ○—○, 1-3, Passage 1/10,000 Mol Morph.; 4-6, Passage 1/5,000 Mol Morph.; 7-10, Passage 1/4,000 Mol Morph.; 11-13, Passage 1/3,300 Mol Morph.; ●—●, M 2, 14-19, Passage 1/2900 Mol Morph.; ×—×, M 1, 14-18, Passage 1/2900 Mol Morph.; +—+, 16-19, Passage morphinfreies Medium.

scheinungen traten auf, als die Zellen in der zweiten Passage mit dieser Dosis behandelt wurden. Die pathologischen Bestandteile verschwanden unter gleichzeitigem Absinken des Wachstums (5. Passage).

Bemerkenswert an dieser Passage war, dass nach 24 Std. fast alle Kulturen noch reichlich Vakuolen hatten und nach 48 Std. die meisten davon frei waren. In dieser begrenzten Zeit musste also eine als Gewöhnung imponierende Stoffwechseländerung eingetreten sein.

Die Konzentration wurde im Laufe einiger Passagen weiter erhöht auf 1/3300 Mol.

Bei der 12. Umsetzung fiel unter 20 Kulturen eine deshalb auf, weil sie nicht— wie alle anderen— mit winzigsten Vakuolen angefüllt war. Diese Kultur wurde zu einer eigenen Beobachtungsreihe entwickelt. Durch ihr besonders gutes Wachstum waren schon in der 15. Passage über 20 Tochterkulturen entstanden. Für diese Reihe war zugesetztes Morphin viel weniger toxisch als für die ursprüngliche. Das zeigen sehr deutlich die Kurven auf Abbildung 1. Von der 12. Passage geht nach oben (M2) das Wachstum der neu entstandenen Reihe resistenterer Kulturen, nach unten (M1) das der parallel laufenden giftempfindlicheren, die bei $1/2900$ Mol abstarben. Die einen wurden also zunehmend grösser, die anderen kleiner als die Kontrollen. Es soll aber darauf hingewiesen werden, dass beide Reihen geschädigt waren, nur die mit M1 bezeichnete viel stärker als die andere. In der M1-Reihe nahmen Verfettung, Granulierung und Vakuolenbildung immer mehr zu. In der M2-Reihe sah man nur winzigste Vakuolen, die den Zellen ein perforiertes Aussehen gaben.

Der Effekt plötzlicher Morphinentziehung ist in der gestrichelten Linie dargestellt. Das Wachstum war nur in einer Passage erheblich geringer, gleichzeitig aber das morphologische Aussehen gegenüber den morphinbehandelten Kulturen viel besser.

Leider musste der Versuch nach der 19. Passage abgebrochen werden, weil sämtliche Kulturen an einer unbekannten Schädigung zu Grunde gingen. Die einzig überlebenden waren die 10 Exemplare, denen vorher das Morphin entzogen war. Deren Wachstum war sogar recht gut. Möglicherweise richtete sich ihre Resistenz nicht nur gegen Morphin, sondern auch gegen andere Schädigungen. Die durchschnittliche Streuung betrug bis zur 12. Passage $\pm 9\%$, in der M1-Reihe $\pm 13\%$ und in der M2-Reihe $\pm 13,5\%$.

B.) *Dolantin* ("Demerol"): (Abbildung 2). $1/10,000$ Mol setzte zunächst das Wachstum herab mit zunehmenden morphologischen Zellveränderungen, wie sie schon im Morphinabschnitt beschrieben sind. Es trat aber allmählich bis zur 7. Passage eine so vollständige Gewöhnung ein, dass weder in der Grösse noch im morphologischen Aussehen ein Unterschied gegenüber den Kontrollen zu erkennen war. Unmittelbar danach kam es zu einem rasch fortschreitenden Verfall. Nach der 11. Umsetzung wurde noch dolantinfreies Medium verwendet, ohne eine Besserung hervorzurufen. Die Möglichkeit relativen Dolantinmangels, wie er oben für die Morphinreihe angedeutet wurde, kann nach der erfolglosen Dosiserhöhung in der 5 und 10. Passage als ausgeschlossen gelten. Das Wachstum wies innerhalb der einzelnen Passagen dieser Reihe eine durchschnittliche Abweichung von $\pm 11\%$ auf.

C.) *Polamidon* ("Methadone"): (Abbildung 3). $1/40,000$ Mol schädigte die Fibroblasten nicht nachweisbar. Bei $1/20,000$ Mol nahm das Wachstum immer mehr ab, die Zellen füllten sich mehr und mehr mit Fett, Vakuolen und Granula. Auch hier wurde relativer Mangel durch erfolglose Dosiserhöhung in der 6. Passage unwahrscheinlich gemacht. Absetzen des Pharmakons nach der 8. Umsetzung führte zu schneller Erholung. Dann wurde beiden Versuchsreihen, sowohl den noch mit $1/20,000$ Mol behandelten als auch den entwöhnten Kulturen, die Dosis von $1/10,000$ Mol verabreicht. Dabei zeigte sich, dass die Giftfestigkeit der ent-

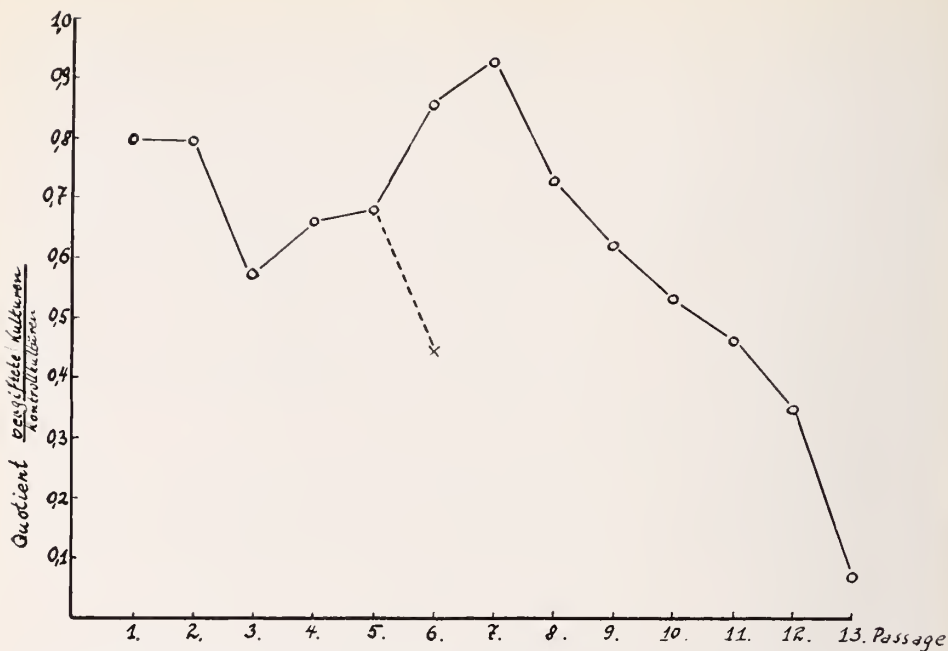


ABBILDUNG 2: ○—○, 1-9, Passage 1/10,000 Mol Dolantin; 10-11, Passage 1/5000 Mol Dolantin; 12-13, Passage Dolantinfreies Medium; ○- -X, 1/5000 Mol.

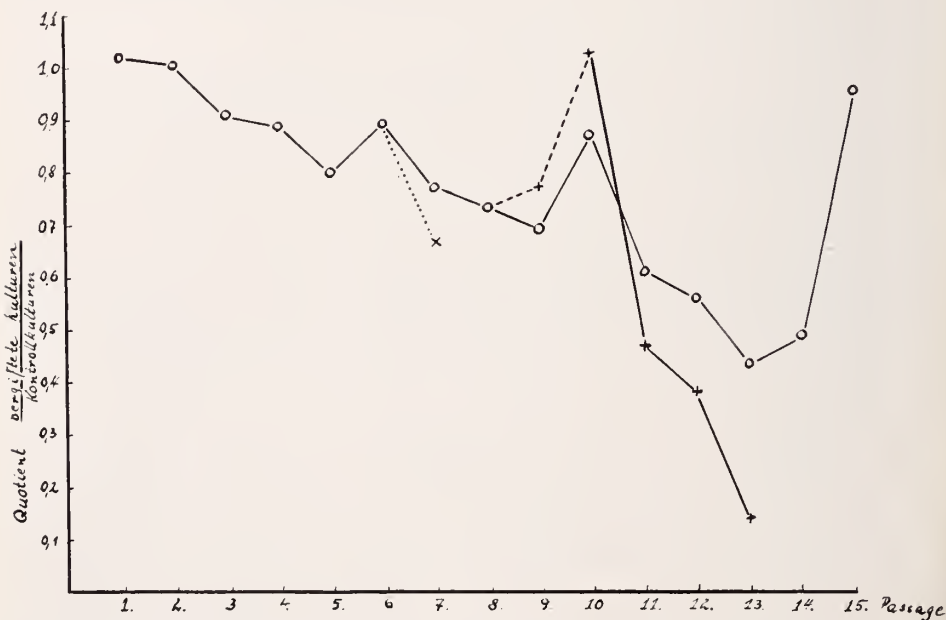


ABBILDUNG 3: ○—○, 1-2, Passage 1/40,000 Mol Polamidon; 3-10, Passage 1/20,000 Mol Polamidon; 11-13, Passage 1/10,000 Mol Polamidon; 14-15, Passage Polamidonfreies Medium; ○ · · · X, 1/10,000 Mol Polamidon; + - - +, Polamidonfreies Medium; ++, 1/10,000 Mol Polamidon.

wöhnten Kulturen geringer war, sie wuchsen schlechter und starben auch nach wenigen Passagen ab. Durch Umsetzen der anderen Reihe in normales Medium trat wiederum vollständige Erholung ein. Die durchschnittliche Abweichung vom mittleren absoluten Wachstum jeder Passage betrug in der Polamidonreihe $\pm 10\%$.

BESPRECHUNG

Unsere Versuche bestätigen die schon angeführten japanischen Arbeiten, nach denen es relativ leicht gelingt, Fibroblastenkulturen an Morphin zu gewöhnen. Dazu ist eine laufende Dosiserhöhung notwendig. Durch plötzlichen Entzug kommt es zum Nachlassen des Wachstums, was man als Abstinenzerscheinung deuten kann. Diese Reaktion fanden wir nicht so ausgeprägt, wie die früheren Autoren, die allerdings im Gegensatz zu uns an Herzfibroblasten arbeiteten. Das könnte die Unterschiede immerhin erklären, denn es ist bekannt, dass Fibroblasten verschiedener Körperregionen sich verschieden verhalten. Ausserdem haben wir aber beobachtet, dass mit der Abnahme des Wachstums eine Normalisierung der Zellstruktur einhergeht. Möglicherweise ist der Rückgang des Wachstums nur vorgetäuscht durch den Schwund der pathologischen Zellbestandteile wie Fett, Granula und Vakuolen. Auf diese Weise erklärt sich wahrscheinlich auch der Anstieg der Kurve M2 auf Abb. 1.

Weiterhin geht aus den Beobachtungen an der Morphinreihe hervor, dass auch in einem einheitlich anmutenden Zellmaterial Zellen vorhanden sind, die erblich bedingt eine höhere Giftfestigkeit besitzen. Anders wäre die Doppelläufigkeit der Kurve kaum zu erklären; handelte es sich dabei lediglich um eine Variation und nicht um eine Mutation, so müssten die Kurven wenigstens nach 3 oder 4 Passagen eine Tendenz zur Annäherung zeigen.

Gewöhnungen an Dolantin und Polamidon sind sehr viel geringer und unseres Erachtens so unspezifisch wie sie Verne (3) für Atropin, Dinitrophenol und Kupfersalze und Vollmer und S. T. Li (4) für Neosalvarsan beschrieben haben.

Nach unseren Beobachtungen ist die Methode der Zellkultur nicht geeignet, über suchterzeugende Eigenschaften Auskunft zu geben. Dagegen sagt sie sehr wohl etwas über die Gewöhnung an Pharmaka aus. Ihre Ergebnisse dürften demonstrieren, dass Gewöhnungsphänomene weitgehend unabhängig sind von der Resorption und Ausscheidung. Durchaus plausibel ist daher die Theorie von Cloetta (1), nach der es sich um eine "allmähliche Angewöhnung des Protoplasmas an das Morphin" handelt. Dass auch hier in einer scheinbar einheitlichen Zellpopulation, wie überall, mit beträchtlichen Differenzen der primären Empfindlichkeit zu rechnen ist, bedarf kaum der Erwähnung.

ZUSAMMENFASSUNG

Fibroblastenkulturen konnten leicht und gut an Morphin gewöhnt werden. Dabei traten in einem primär einheitlichen Zellmaterial sehr verschieden empfindliche Modifikationen auf. Für das "Entziehungsphänomen" wird eine Erklärung zu geben versucht.

An Dolantin und Polamidon lassen sich Zellkulturen nur in geringem Grade gewöhnen.

SUMMARY

Tolerance for morphine can be easily produced in tissue cultures (fibroblasts from legs of chick embryos) confirming the work of Sasaki and Kubo. Although these cultures were of the same origin great differences in resistance were encountered in subsequent passages.

An attempt is made to explain the phenomenon of withdrawal. Demerol (Dolantin) and Methadone (Polamidon) produce little tolerance in tissue cultures.

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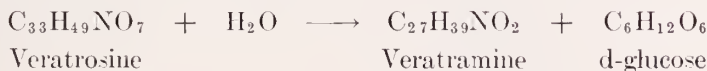
ANTIACCELERATOR CARDIAC AGENTS*

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In the survey of substances capable of blocking the effects of the stimulation of various autonomic nerves upon their effectors, no agents had come to light during the past 100 years which were capable of exerting in the mammalian heart a selective blocking action on the cardioaccelerator effect of sympathomimetic amines or of accelerans stimulation. This action apparently rests upon a peculiar biochemical property of the automatic tissue of the mammalian heart which requires a chemical counterpart not hitherto met with among natural (or synthetic) compounds. The recent finding that certain alkaloids of steroid nature, or related to it, exhibit such highly selective blocking action on the cardioaccelerator mechanism bears out this assumption (1, 2, 3). Substances with this property were first found among the naturally occurring veratrum alkaloids, *e.g.* veratramine, veratrosine, jervine and pseudojervine. The recognition of these alkaloids as selective blocking agents of the cardioaccelerator mechanism of the mammalian heart closes an important gap in the general scheme of the pharmacology of the autonomic system.

The veratrum alkaloids veratramine, veratrosine, jervine and pseudojervine are secondary amines. Veratramine and jervine are the genins of the glycosidic compounds veratrosine and pseudojervine.



In the past, the pharmacological studies of the veratrum alkaloids were devoted almost exclusively to crude preparations made from the plants, to unknown mixtures of alkaloids, or to the group of pure alkaloids which are now known to be esters of tertiary alkamines. The most important of these ester alkaloids and their origin and composition are given in Figure 1. The available evidence indicates that the tertiary veratrum alkamines or their esters do not possess the pharmacological property to be described below.

1. *The antiaccelerator action of the secondary veratrum alkaloids.* The name jervine appears in the literature in 1837 and was first applied in 1879 to a pure alkaloid, isolated by Wright and Luff from *Veratrum viride* and *Veratrum album* (4). Pseudojervine was found also in 1879 by Wright and Luff. Veratramine

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and veratrosine, on the other hand, have been known only for a few years; the former was first isolated by Sato in 1940 (5), the latter by Jacobs and Craig in 1944 (6). Although jervine has been the subject of pharmacological study as early as 1874 (7), it is not surprising that the peculiar nature of its action upon heart rate should have been overlooked. Superficially, the heart rate decreasing action in the intact animal, as well as the vasodepressor action, and the central nervous system stimulating action, appeared similar to the actions upon the same systems of the veratrum ester alkaloids of Figure 1 (8). That there was something peculiar about the negative chronotropic cardiac action of jervine, and of the other alkaloids chemically related to it, which puts these secondary amines into a group of pharmacological agents different from that of the tertiary alkamines

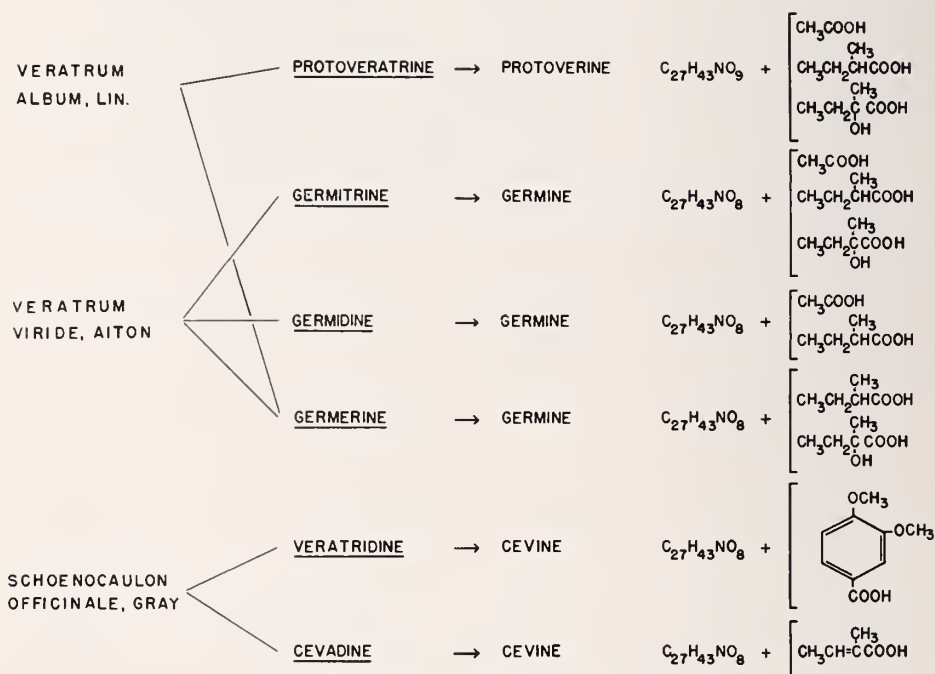


FIG. 1. *Veratrum* ester alkaloids

and their esters, could only be recognized under very special experimental conditions. These were fulfilled by chance, when epinephrine was administered to the failing heart of a heart-lung preparation, which had been treated with veratramine in the erroneous assumption that veratramine and jervine might have a positive inotropic action like cevine and veratridine. It was then noticed that epinephrine in a dose usually leading to a marked increase in heart rate did not produce its customary cardioacceleration, although its action upon output was not noticeably changed in intensity or duration (fig. 2). It was a further favorable circumstance that this original observation was made with veratramine, the most potent substance of this new group of pharmacological agents, and not with the much weaker jervine.

Even in a heart-lung preparation the continuously changing heart rate after single injections of epinephrine or norepinephrine does not provide the most favorable condition for the unequivocal demonstration of antagonistic action on the cardioaccelerator effect of these sympathomimetic amines. Steady state conditions of heart rate increase are required. They can be satisfactorily produced by continuous infusion of the rapidly decaying substances. With a rate of infusion of 3 microgm. per minute of *l*-epinephrine or *l*-norepinephrine base into

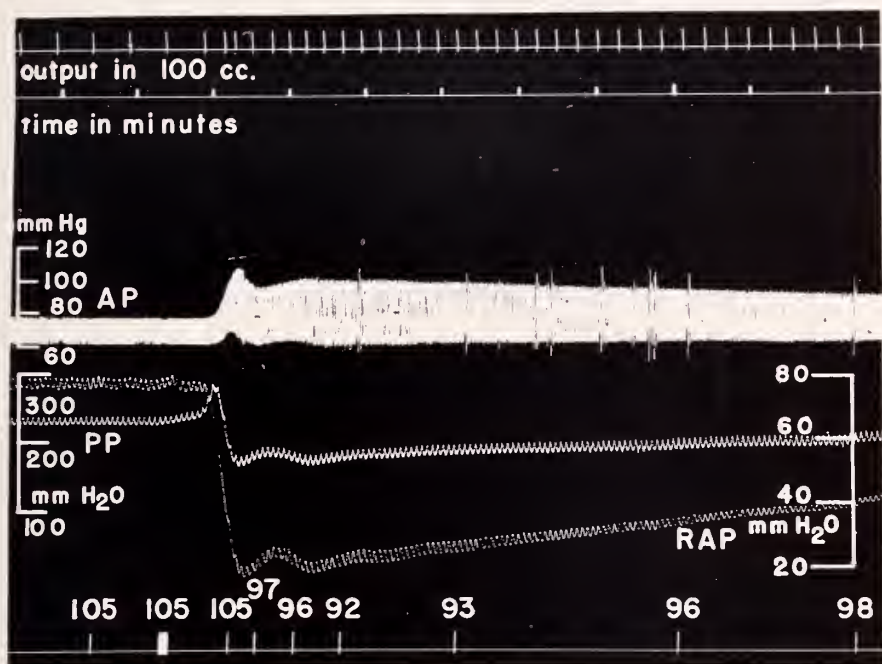


FIG. 2. The positive inotropic action of epinephrine (after veratramine) in the absence of positive chronotropic action. Dog, male, 11.6 kgm. Heart-lung preparation (December 3, 1948). From top to bottom: Systemic output (total output of left ventricle minus coronary flow) measured by Weese stromuhr in 100 cc./stroke. Time in minutes. AP: arterial pressure recorded with Hg manometer, calibration on left in mm. mercury. PP: (lower curve on left—middle curve on right): pulmonary pressure recorded with bromoform manometer, calibration on left in mm. water. RAP: (middle curve on left, lower on right): right atrial pressure recorded with water manometer, calibration on right in mm. water. Horizontal row of figures: heart rate per minute. Temperature of the blood varied between 38.5 and 38.8° C. Total blood volume was approximately 500 cc. At the broad signal 10 microgm. of epinephrine were injected close to the heart. 8.5 mgm. veratramine had been given in divided doses during 2 hours preceding the epinephrine administration. (Reprinted from the *Journal of Pharmacology and Experimental Therapeutics*, Volume 96: 422, 1949.)

a heart-lung preparation a convenient heart rate increase is obtained and a steady level of acceleration is usually reached within 30 minutes (fig. 3). Adequate doses of veratramine, veratrosine, jervine or pseudojervine are capable of antagonizing the accelerator effect completely and can restore the rate to normal values in spite of the continuing administration of the respective sympathomimetic amine. While veratramine and jervine decrease the heart rate abruptly, leading to the maximal effect within one to two minutes after the injection, the full effect of

their glucosides, veratrosine and pseudojervine, develops slowly. Figure 3 shows the action of the genin veratramine and of its glucoside veratrosine in representative experiments. The experiment with veratrosine illustrates the fact, and this is true for all the alkaloids of this group, that the heart rate decreasing action is not prevented or abolished by atropine. The segment of the vagal system, remaining in functioning condition in the isolated heart after severing the vagus nerve in the neck, does not participate in this reaction.

Under the conditions indicated, the heart rate, as a rule, remains a regular sinus rhythm, as it is decreased over the whole range of acceleration to or near the initial rate prior to the administration of epinephrine. In some cases the rate is diminished to a level below the initial rate. Doses beyond a certain range not

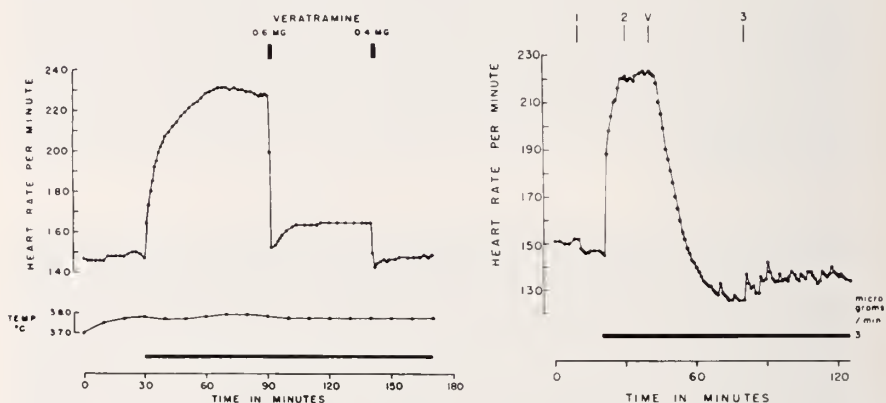


FIG. 3. *The antiaccelerator cardiac action of veratramine and of veratrosine. Left: Dog, male, 11.0 kgm. Heart-lung preparation (March 7, 1951). Total blood volume 800 cc. Mean arterial pressure 108 mm. Hg. Systemic output per min. 450 cc. Temperature varied between 37.0 and 37.9°C. Ordinate: heart rate per minute. Abscissa: time in minutes. The black bar indicates infusion of 3 microgm. of *l*-epinephrine base per minute (as bitartrate). At the signals 0.6 and 0.4 mgm. veratramine, respectively, were injected within two minutes. Right: Dog 9.3 kgm. Heart-lung preparation (March 6, 1949). Total blood volume 700 cc. Mean arterial pressure 114 mm. Hg. Systemic output approximately 500 cc. per min. Temperature varied between 38 and 38.9°C. Atropine sulfate injections: 5 mgm. each at 1 and 2, and 10 mgm. at 3. At V, 1 mgm. veratrosine was injected. There is a one-minute time interval between successive points of the heart rate curves from the beginning of the effect of the two veratrum alkaloids to the lowest heart rate reached.*

only do not cause further decrease in rate but lead to irregularities of rate and rhythm and often to heart rate increase. The nature of these changes, caused by large doses, is not at present understood.

In the presence of one of the alkaloids of the veratramine group the automatic tissue of the heart has not lost its ability to respond with an increase in the rate of impulse generation to an increase in epinephrine concentration, rather it becomes less responsive to this pharmacological stimulus. In the experiment of Figure 4 the dose of 0.3 mg. of veratramine caused a decrease in heart rate of more than 50 per cent of the acceleration produced by the continuous infusion of 3 microgm. of *l*-epinephrine base per minute, but inhibition of acceleration was not complete. This inhibitory action could be overcome by an infusion rate of approximately 30 microgm. of epinephrine per minute.

The antagonistic action is not restricted to the cardioaccelerator effect of epinephrine and norepinephrine but the positive chronotropic effect of several other aromatic as well as aliphatic sympathomimetic amines, tested so far, was also antagonized. In Figure 5 the effect of veratramine upon the cardioaccelerator effect of ephedrine is shown. Successive and increasing doses of veratramine amounting to the total dose of 6 mgm. eventually abolished the effect of 3 mgm. of ephedrine.

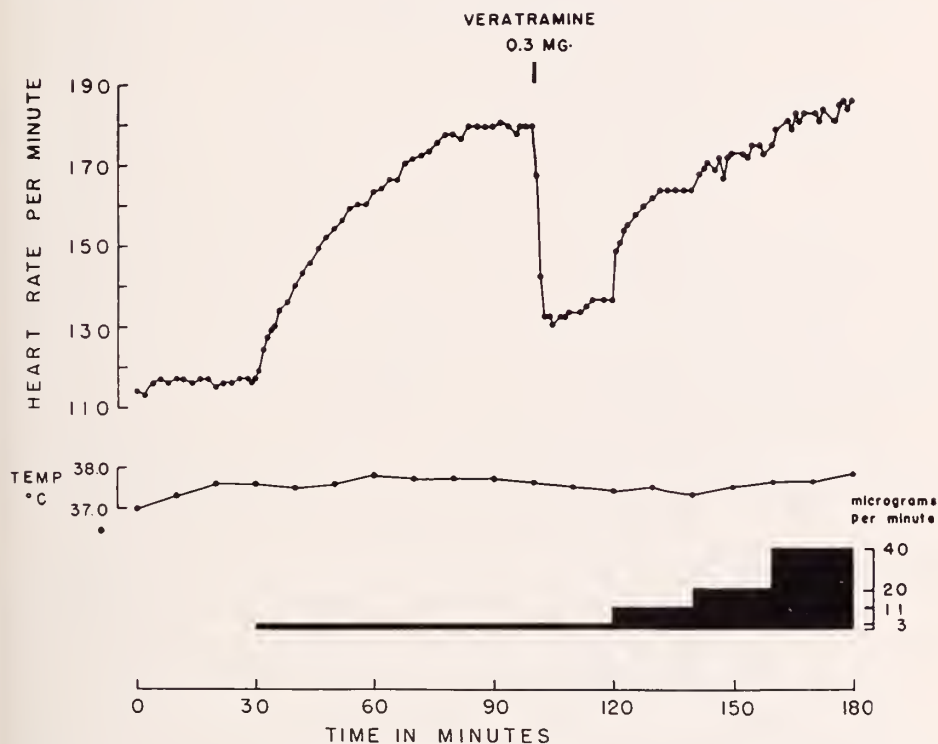


FIG. 4. The antiaccelerator action of veratramine and the antagonistic effect of increasing concentrations of epinephrine. Dog, female, 10.5 kgm. Heart-lung preparation (December 7, 1950). Total blood volume 850 cc. Mean arterial pressure 100 mm. Hg. Systemic output approximately 500 cc. per min. Temperature varied between 37 and 37.8° C. Ordinate: Heart rate per minute. Abscissa: Time in minutes. At the signal, 0.3 mgm. of veratramine was injected in two minutes. Black bar: continuous infusion of *l*-epinephrine base 1:5000. Calibration at right in micrograms per minute.

It was of special interest to show the antagonistic action of veratramine and of the related alkaloids under conditions of heart rate increase caused by electrical stimulation of the accelerans nerve (9). When in the heart in situ (spinal cat, heart acutely denervated) stimulation of the postganglionic adrenergic fibers from one stellate ganglion to the heart has increased the heart rate, a precipitous fall in rate is caused by veratramine. The pacemaker becomes insensitive to indirect stimulation immediately after administration of appropriate doses of veratramine and regains its responsiveness to indirect stimulation only very gradually. In the light of the experiments with epinephrine and norepineph-

rine on the isolated heart, it is reasonable to assume that the automatic tissue becomes insensitive to the release of the sympathomimetic amines involved in the transmission of accelerator impulses. It remains to be shown conclusively, however, that veratramine does not interfere with the release of the transmitter substance or substances.

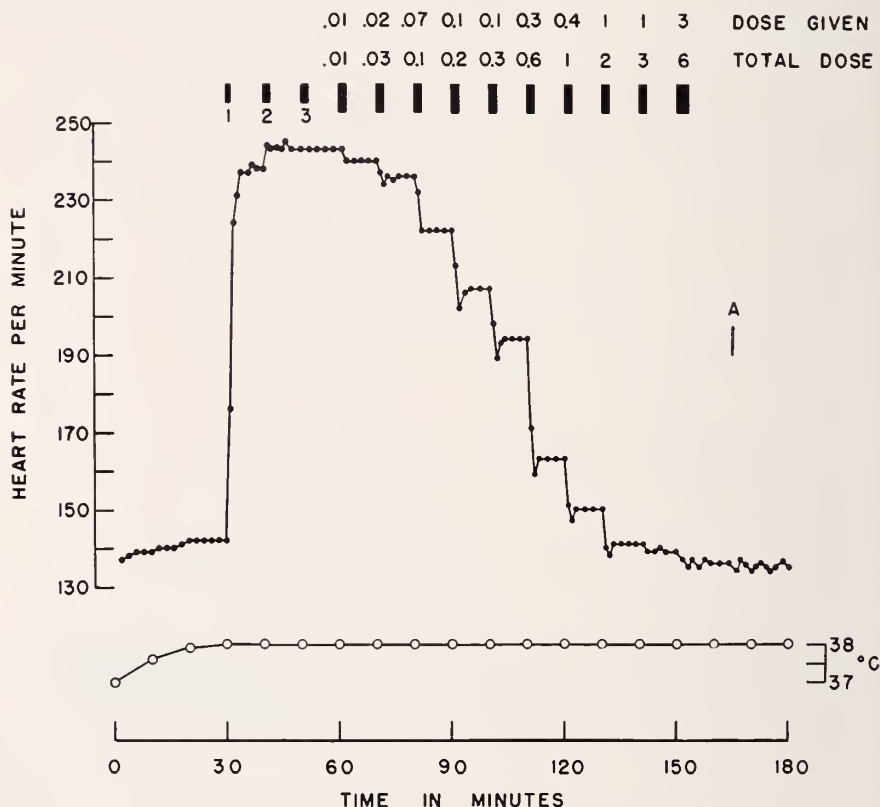


FIG. 5. *The antagonistic action of veratramine to the cardioaccelerator effect of ephedrine.* Dog, male, 8.2 kgm. Heart-lung preparation (November 29, 1950). Total blood volume 850 cc. Mean arterial pressure 110 mm. Hg. Systemic output approximately 500 cc. per min. Ordinate: Heart rate per minute. Abscissa: Time in minutes. At 1, 2 and 3, ephedrine sulfate (1 mgm. of the base) was injected each time. At the following signals, veratramine was injected; the top row of figures gives the dose actually administered; the bottom row indicates the total dose of veratramine given up to and including the respective single injection. At A, 10 mgm. of atropine sulfate was injected.

When there is an elevated rate with regular sinus rhythm caused by the action of sympathomimetic amines, the changes in rate observed under veratramine point to the sino-auricular node as the site of action. Studies now underway indicate that subsidiary pacemakers in the Purkinje tissue, for example, in the atrial tissue outside the area of the sino-auricular node, or in the atrioventricular node, are also susceptible to the effect of veratramine when their automatic activity is increased by the administration of sympathomimetic amines. In ventricular tachycardia, produced by epinephrine in the presence of cyclopropane in dogs, veratramine has proved incapable of abolishing the tachycardia.

In two cases of spontaneous auricular flutter, observed in heart-lung preparations during the initial stage of the experiment and prior to any drug administration, veratramine in doses up to 1 mgm. was unable to terminate the flutter (11). In the presence of veratramine which has led to a marked decrease in responsiveness of the sino-auricular node to the effects of epinephrine, heart rate can still be increased readily by increasing locally the temperature of the pacemaker tissue. The available evidence (10) suggests that there is no quantitative difference in this cardioacceleration by heat before and after the administration of veratramine. The mechanism involved in this kind of cardioacceleration obviously is not influenced by veratramine.

The heart rate decrease produced by veratramine is shown in its most striking form when there is cardioacceleration caused either by the administration of sympathomimetic amines or by accelerans stimulation in which, presumably, sympathomimetic amines are also involved. The heart rate decrease is due not to an increase in decelerator activity but to a decrease in the sensitivity of the pacemaker tissue to the accelerator effects of the sympathomimetic amines. Therefore, the negative chronotropic action of the alkaloids of the veratramine group has been designated "antiaccelerator action" to distinguish it from other negative chronotropic actions, such as the decrease in heart rate by temperature decrease, or by vagal stimulation, or by the action of parasympathomimetic substances, in which a block of the action of sympathomimetic amines obviously is not involved (10).

2. *The selectivity of the antiaccelerator cardiac action.* It was mentioned above that pretreatment with veratramine can prevent cardioacceleration by epinephrine in the mammalian heart without preventing the influence of the sympathomimetic amine upon the force of contraction leading to an increase in the work capacity of the heart. A rigorous proof of the possibility to separate the positive chronotropic from the positive inotropic action of epinephrine is given in the experiment of Figure 6. A heart-lung preparation was arranged so as to have a systemic output of 670 cc. per minute at the basal condition of blood supply. A competence test 1, by changing the load of volume work of the heart, indicated that a two step increase in blood supply resulted in an output increase to 875 cc/min. and 1100 cc/min. respectively. Since the increase in blood supply was made by lifting the level of the blood in the venous reservoir at each step by 50 mm. above the basal level, and since the right atrial pressure rose only a few millimeters, for every 50 mm. rise in the reservoir level, the output of 1100 cc/min. was still far below the limit of competence of this heart.

After basal blood supply had been restored, heart failure was produced by adding sodium pentobarbital to the blood. The basal output dropped to 475 cc/min. and the competence test 2 indicated that the output could no longer be increased by increasing the blood supply. (It actually fell to 400 cc./min.) Rate had not changed and the heart volume was much increased, indicating that the heart worked with a great diastolic fiber length but was incapable of working with its basal (pre-failure) stroke volume.

Continuous infusion of epinephrine increased the output of the heart somewhat above the initial basal output (720 cc.), while at the same time the heart rate

rose from 140 to 200 beats per minute. The competence test 3 showed that the volume work capacity was fully restored. The heart, however, worked with a low stroke volume owing to the marked acceleration of heart rate. The administration of 0.5 mgm. of veratramine promptly decreased the heart rate to 148

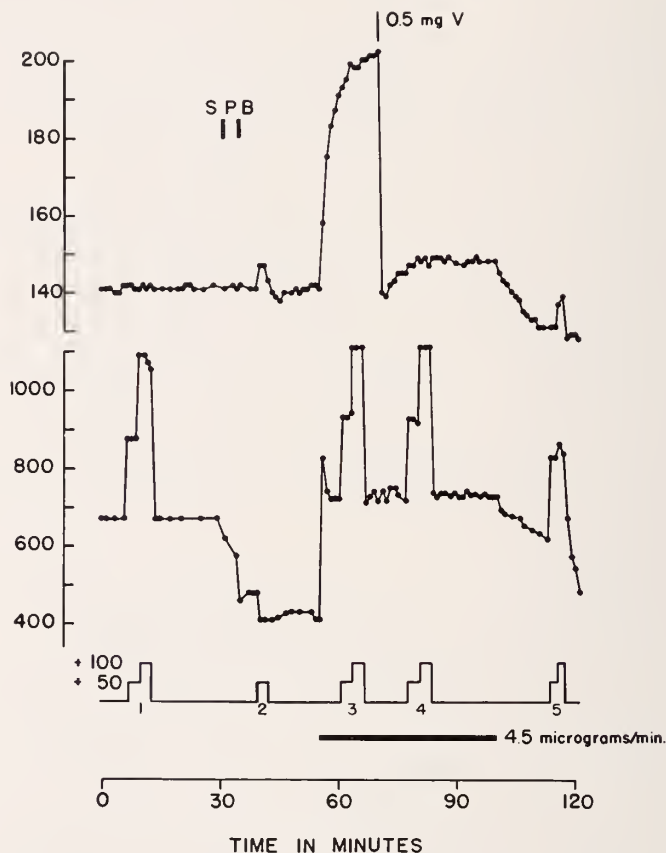


FIG. 6. Separation of the positive inotropic action from the positive chronotropic action of epinephrine. Dog, female, 10.9 kgm. Heart-lung preparation (February 28, 1950). Total blood volume 700 cc. Mean arterial pressure 112 mm. Hg. The temperature varied between 37.5 and 38° C. From top to bottom: Heart rate in beats per minute (ordinate); systemic output in cc. per minute (ordinate); changes of level of blood in the supply vessel (+50 and +100 means that the reservoir blood level was raised to 50 or to 100 mm. respectively above basal level. The black bar indicates continuous infusion of 4.5 microgm. of *l*-epinephrine base per minute. At S.P.B., 75 mgm. sodium pentobarbital was added to the heart-lung preparation to cause myocardial failure. At the signal 0.5 mgm. V. Veratramine was injected. Seven minutes after stopping the epinephrine infusion 350 cc. of blood were removed and 420 cc. of blood (containing no epinephrine!) were substituted in order to hasten the decrease in epinephrine concentration. For further explanation see text.

beats per minute, or slightly above the normal initial rate, thus restoring the initial conditions of stroke volume without changing basal output or influencing the competence test 4. It could be shown in other experiments (12) that when there is a decrease in heart rate, due to the antiaccelerator action of veratramine,

there is also a decrease in total oxygen consumption. The effect of veratramine in the experiment of Figure 6, therefore, must have resulted in an increase in efficiency of the heart, a change which is not revealed by the competence test.

Upon discontinuation of the epinephrine infusion its concentration decreased due to the destruction of the substance and due to the exchange of some of the blood. Failure returned as indicated by the drop in the basal output and by the poor response of the heart to the competence test 5.

Epinephrine strikingly shortens the functional and absolutely refractory periods of A-V transmission and the A-V propagation time. Just as veratramine is incapable of modifying the positive inotropic action of epinephrine, so it is incapable of preventing or abolishing the effect of epinephrine on the functional and absolutely refractory periods of A-V transmission, and on A-V propagation time, in a dosage range in which the cardioaccelerator effect is markedly decreased or completely abolished (13).

In order to obtain conclusive evidence as to whether or not the alkaloids of the veratramine group have an antagonistic action on the vaso motor effect of epinephrine or norepinephrine, it is best to use the spinal preparation of the cat, since veratramine, for example, has a strong central nervous system stimulating action when the brain is intact (1, 2, 3). If doses of 0.3 mgm. per kgm., or more, are given to dogs or cats in anesthesia, convulsions may break through the depression of the higher areas of the central nervous system, while no convulsant effects originating in the spinal cord are noticed when doses of the same order are given to the spinal cat. As the experiment of Figure 7 shows, veratrosine (and this is true of the other secondary veratrum alkaloids) is incapable of abolishing the vasopressor effect of a continuous infusion of *l*-epinephrine and *l*-norepinephrine in a dosage which largely abolishes, at least temporarily, the cardioaccelerator effect. It is noteworthy that this occurs although the secondary veratrum alkaloids possess some vasodepressor activity, the nature of which is as yet not properly clarified.

The motor effects of epinephrine on other effectors of the autonomic system have not yet been fully explored in regard to the antagonistic action of veratramine. In the uterus of the non-pregnant rabbit no antagonistic action is seen. The motor effect of epinephrine upon the nictitating membrane of the cat, as well as the motor effect of the stimulation of its sympathetic nerve, is antagonized (14).

The inhibitory effect of epinephrine upon the gut, using the isolated strip of the small intestine of the rabbit, is not characteristically modified by veratramine (11).

3. *The quantitative determination of antiaccelerator activity.* In the intact dog and cat or in the spinal cat the action of a single effective dose of veratramine does not persist. It decreases noticeably within one hour. In the heart-lung preparation of the dog, however, a single dose once administered appears to exert its effect for the few hours of the lifetime of the preparation.

It seemed possible, therefore, to use the heart-lung preparation for the quantitative determination of antiaccelerator potency after the heart rate had been

increased by administering an arbitrarily selected dose of epinephrine by continuous infusion, thus obtaining a standard degree of cardioacceleration under otherwise constant conditions of blood pressure, temperature, total blood volume and systemic output. The persistence of the effect of a single dose of an antiaccelerator agent, like veratramine, makes it possible to obtain appropriate increments of antiaccelerator effect by adding increasing doses of the substance to the heart-

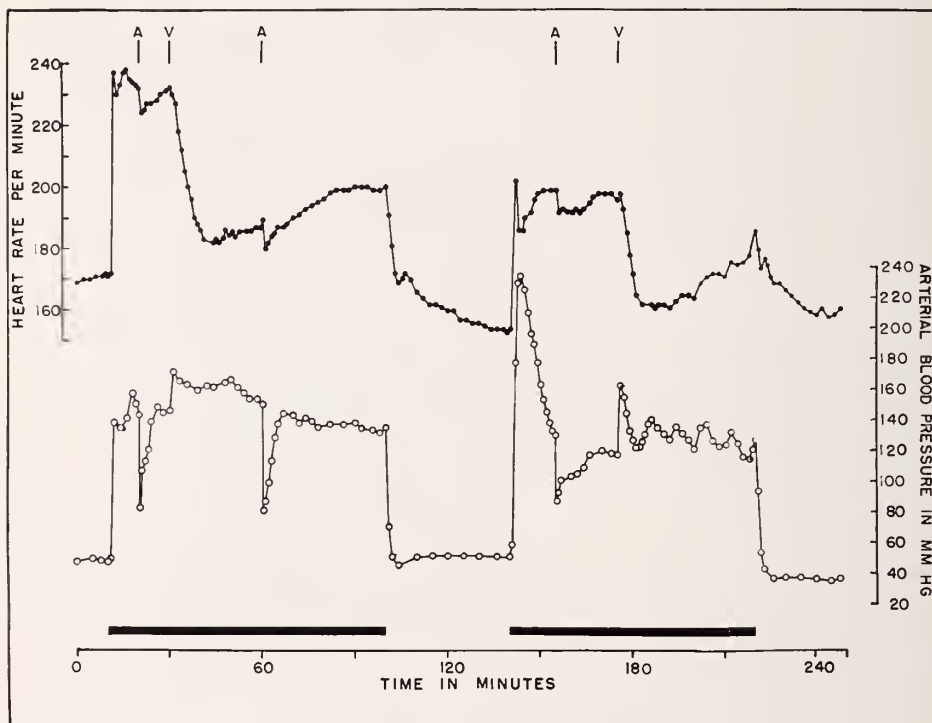


FIG. 7. The effect of veratrosine on heart rate and blood pressure during continuous infusion of epinephrine and norepinephrine in the presence of atropine. Cat, male, 3.65 kgm. Spinal preparation. The blood pressure was recorded from the left carotid artery with a mercury manometer. The rectal temperature varied between 39.1 and 40.0° C. Black bars: continuous infusion of *l*-epinephrine (1:1000) 3 microgms. per kgm. per minute (first half of the experiment); and *l*-norepinephrine (1:1000) 3 microgms. per kgm. per minute (second half of the experiment). At V, 0.2 mgm. veratrosine per kgm. was injected intravenously. At A, 10 mgm. atropine sulfate were injected intravenously. 3 hours and 5½ hours, respectively, prior to the beginning of this experiment, two doses of 0.2 mgm. veratrosine per kgm. had been administered.

lung preparation until the total dose suffices to completely inhibit the cardioacceleration (10). An experiment of this kind is shown in Figure 8 left. A steady state of cardioacceleration was established, corresponding to the continuous infusion of 3 microgm. per minute of *l*-epinephrine base. The antiaccelerator agent (dihydrosolasodanol, see Figure 10 and also Table 1) was then administered at 10 minute intervals and in the doses given in the top row of figures. The first dose was ineffective, the subsequent doses caused greater and greater de-

degrees of inhibition of acceleration; with the final dose of 5 mgm., or a total final dose of 15 mg., the accelerator effect of 3 microgm. of epinephrine per minute was completely antagonized. If the total decrease in rate, from the level of maximal acceleration to the initial rate prior to the epinephrine infusion, is considered to represent 100 per cent inhibition of acceleration, then each level of heart rate, obtained with successive doses of the antiaccelerator compound, represents a definite fraction of the total inhibition; and each fractional inhibition, in the light of what has been stated above, can be considered to be due to the total dose administered prior to reaching each new level of inhibition. In Figure 8 right, the probits of the values of percentage fractional inhibition, between 20 per cent and 80 per cent, have been plotted against the logarithms of the re-

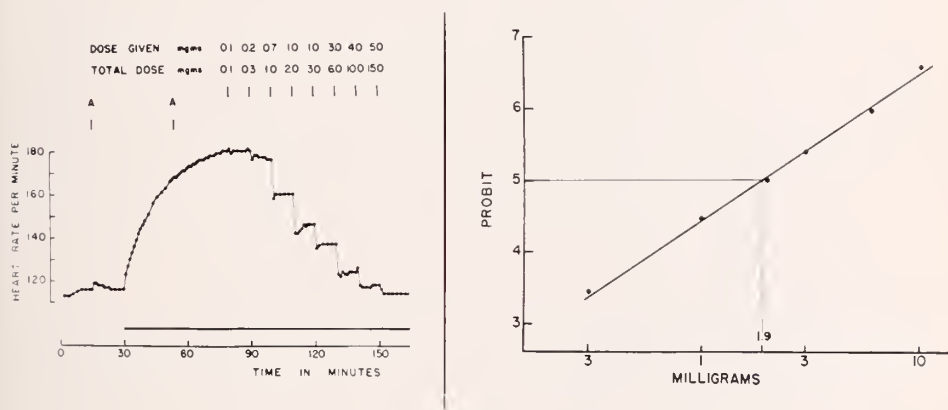


FIG. 8. The graded inhibition by dihydrosolasodanol of the cardio-accelerator action of epinephrine in the isolated mammalian heart. Dog, male, 9.2 kgm. Heart-lung preparation (November 23, 1949). Blood volume 900 cc. at the beginning. Temperature varied between 39.6 and 39.9° C. Mean arterial pressure 110 mm. Hg. Systemic output 500 cc. per minute. Left: Dihydrosolasodanol solution 1:2000 in 5 per cent glucose was administered in increasing doses. The top row of figures indicates the single doses (0.1 to 5.0 mgm.) actually given at the respective signals. Below are the total doses (0.1 to 15.0 mgm.) given up to and including the respective single doses. At A, 10 mgm. of atropine sulfate were injected. Black Bar: continuous infusion of *l*-epinephrine (1:5000); at the rate of 3 microgm./min. Right: Probit plot of experimental data, for explanation see text.

spective total doses. From this plot the dose causing 50 per cent inhibition ($I_{50} = 1.9$ mgm.) could easily be obtained. In spite of considerable variations in initial rate, and in acceleration caused by the standard dose of epinephrine, I_{50} values in a series of experiments with a single substance do not differ excessively, considering the nature of the experiments. The degree of variation is illustrated in Figure 9, in which the percentage inhibition of acceleration caused in 6 experiments by tetrahydrojervine, is plotted against the log dose. On the basis of such observations the mean I_{50} value from a series of 5 to 7 experiments has been accepted as a satisfactory figure for a quantitative comparison of anti-accelerator activity.

4. *The chemistry of the antiaccelerator agents.* As was stated above, the naturally occurring veratrum alkaloids which display antiaccelerator activity are *secondary*

amines; while the alkaloids of the veratrum series responsible for the characteristic myotonic, vasodepressor, and cardiodecelerator action, are esters of *tertiary* amines.

The skeletal structure of the secondary alkamines, veratramine and jervine, is not as yet fully known. It may be considered closely related to that of the tertiary alkamines, some of which are of steroid nature, since the degradation products are identical with those obtained from the tertiary bases. Concerning the position of the nitrogen, the evidence is conclusive that in the secondary alkamines, veratramine and jervine, this is present in the form of a piperidine

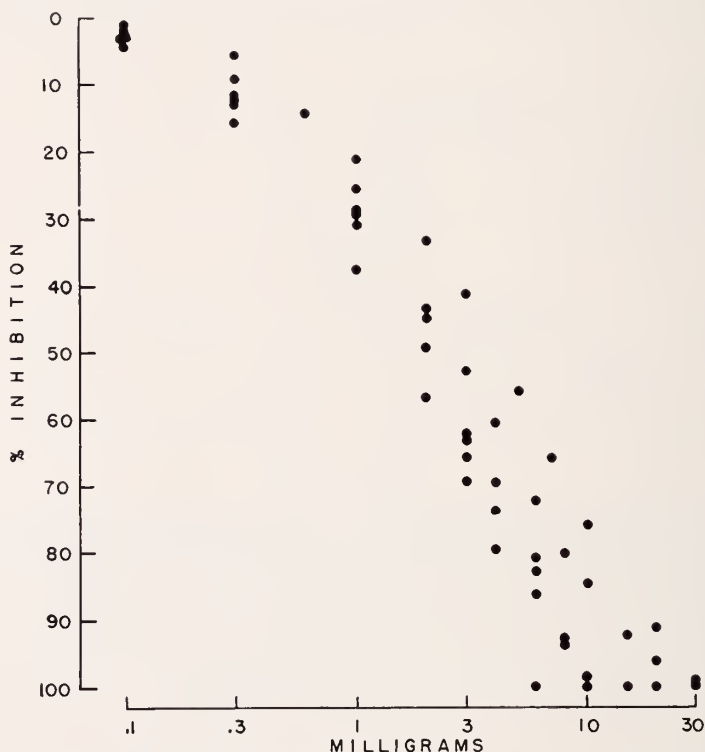


FIG. 9. *The antiaccelerator potency of tetrahydrojervine.* Heart-lung preparations of six dogs. Cardioacceleration was uniformly produced by continuous infusion of 3 microgm. of *l*-epinephrine base per minute. Ordinate: percentage inhibition of acceleration. Abseissa: dose of tetrahydrojervine in milligrams.

ring, while in the tertiary alkamines it is present in the form of an octahydro-pyrrocoline nucleus.

All the substances, hitherto investigated (15), with an antiaccelerator activity of the order of that of jervine or higher, have been piperidine derivatives (Table 1). That the piperidine ring is of importance is strikingly shown by the hundred-fold increase in potency which obtains when the secondary solanum alkamines solasodine and solasodanol, for which a spiroaminoketal structure has been suggested, are transformed by hydrogenation to the piperidine type compounds dihydrosolasodenol or dihydrosolasodanol (Figure 10). Hydrogenation leading

TABLE 1

*The antiaccelerator cardiac activity of steroid secondary alkamines in the heart-lung preparation of the dog**

SUBSTANCE	NUMBER OF EXPERIMENTS	I_{50}^{\dagger} MGM. MEAN \bar{x}	STANDARD DEVIATION OF MEAN $s \bar{x} (\pm)$	RELATIVE POTENCY (MOLAR)
Veratramine.....	7	0.193	0.0169	100
Dihydroveratramine.....	5	0.343	0.0474	57
Dihydrosolasodanol.....	5	1.80	0.236	11
Tetrahydrojervine.....	5	2.33	0.346	9
20-(5'-methyl-2'-piperidyl)- Δ^5 -pregnen-3 β ,20-diol.....	6	6.80	0.90	3
Jervine.....	5	9.68	1.56	2

* Cardioacceleration was caused by the continuous infusion of 3 microgm. of *l*-epinephrine base per minute.

$\dagger I_{50}$: dose causing 50 per cent inhibition of cardioacceleration. The "t" test indicates a significant ($p < 0.01$) difference between veratramine and dihydroveratramine, between dihydroveratramine and tetrahydrojervine, between tetrahydrojervine and jervine; no significant difference exists between dihydrosolasodanol and tetrahydrojervine, or between 20-(5'-methyl-2'-piperidyl)- Δ^5 -pregnen-3 β ,20-diol and jervine ($p > 0.1$).

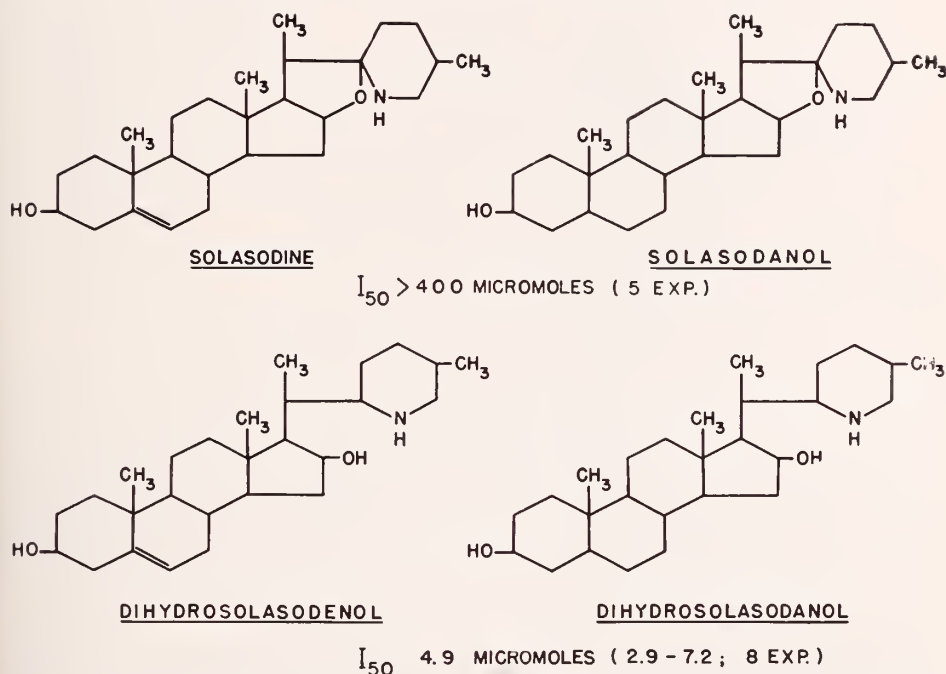


FIG. 10. Structural formulae and antiaccelerator potency of solasodine and its hydrogenation products. I_{50} = dose causing 50 per cent inhibition of cardioacceleration (in the heart-lung preparation of the dog) caused by continuous infusion of 3 microgm. of *l*-epinephrine base per minute.

from solasodine to solasodanol, or from dihydrosolasodenedol to dihydrosolasodanol, on the other hand, does not change potency (16).

Differences in the functions of the main nucleus, however, must account for differences in potency even among piperidine compounds, as evidenced by the fiftyfold greater antiaccelerator potency of veratramine as compared to jervine, and by the influence of hydrogenation upon the potency of veratramine and jervine. Tetrahydrojervine (see also Figure 9), a hydrogenation product of jervine, is approximately three times more potent than jervine. Dihydroveratramine, obtained by hydrogenation from veratramine, has only one-half of the potency of veratramine. It is of interest that its overall toxicity, tested by intravenous injection in mice, is greater than that of veratramine, indicating that in this case toxicity and antiaccelerator activity did vary independently of each other. This is also illustrated by the marked difference in overall toxicity between the glucosides, veratrosine and pseudojervine, and their respective genins, veratramine and jervine. The hydrolysis of the glucosides does not materially change antiaccelerator potency while toxicity increases (10, 17).

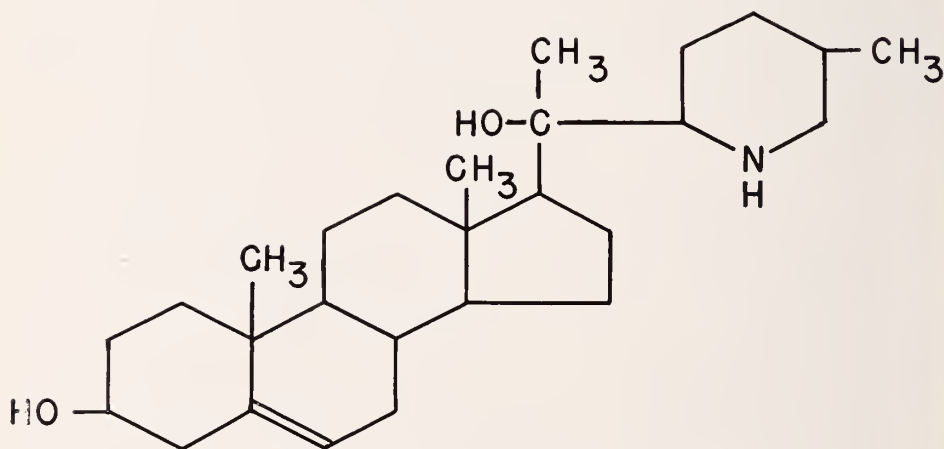


FIG. 11. 20-(5'-methyl-2'-piperidyl)- Δ^5 -pregnen-3 β ,20-diol

On the basis of the chemical knowledge gained from the natural compounds with antiaccelerator activity, successful attempts were made to obtain antiaccelerator compounds by partial synthesis. Of the compounds prepared so far, the most potent one was obtained using pregnenolone as starting material and transforming it into a piperidine derivative, 20-(5'-methyl-2'-piperidyl)- Δ^5 -pregnen-3 β ,20-diol (Figure 11) (15, 18). It exhibits the characteristic property in the heart-lung preparation (Figure 12). Quantitatively it has the same potency as the naturally occurring veratrum alkaloid jervine (see Table 1).

It was pointed out above that solasodine, a secondary amine of spiroaminoketal structure, has only about one thousandth of the antiaccelerator activity of veratramine. An isomer of the piperidine type compound, dihydrosolasodanol, kryptogenamine, was found to have an activity of approximately one three hundredth of that of veratramine. This substance is a steroid secondary amine of the pyrrolidine type (15).

Activity of this low order has been encountered among alkaloids not chemically related to the substances mentioned so far. An interesting example is the anti-accelerator activity of the cinchona alkaloids quinine and quinidine, which have one five hundredth of the potency of veratramine (19). In regard to the mammalian heart, the literature is controversial on the antiaccelerator ("adrenolytic" and "sympatholytic") activity of the ergot alkaloids. The quantitative method

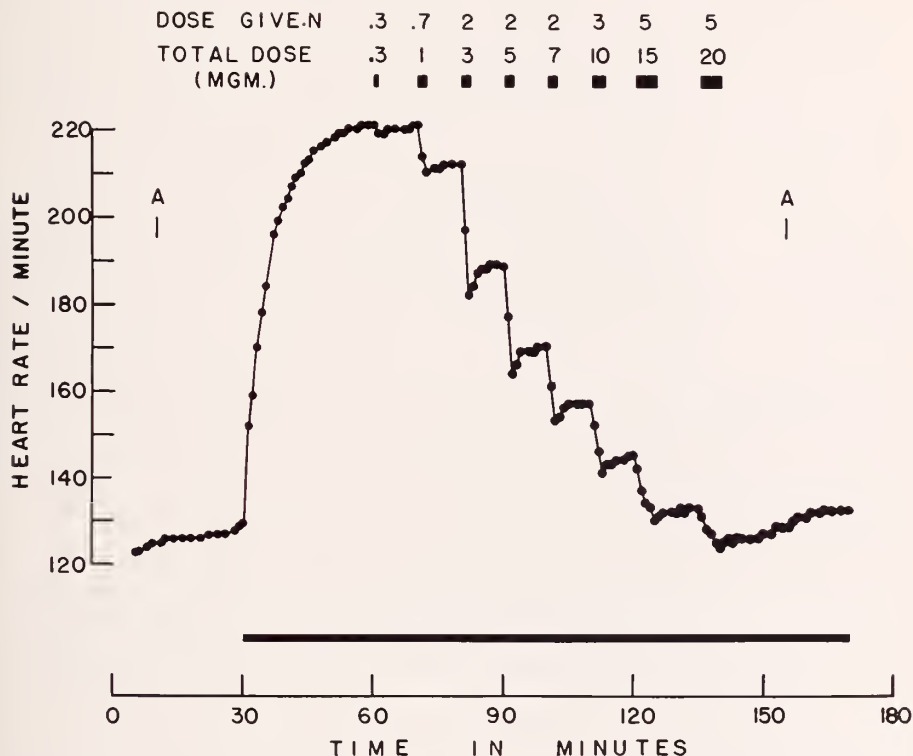


FIG. 12. The antiaccelerator activity of 20-(5'-methyl-2'-piperidyl) Δ^5 -pregnen-3 β , 20-diol. Dog, male, 11.4 kgm. Heart-lung preparation (June 9, 1950). Total blood volume 800 cc. Mean arterial pressure 120 mm. Hg. Systemic output approximately 500 cc. per minute. Temperature of the blood 39° C. Ordinate: Heart rate per minute. Abscissa: Time in minutes. Black bar: continuous infusion of *l*-epinephrine base 3 microgm. per minute. At A, 10 mg. atropine sulfate was injected. The antiaccelerator compound was given at the signals in the doses in mgm. indicated in the top row of figures. The bottom row of figures gives the total doses up to and including the respective given dose. The width of the signal indicates the time taken to complete the injection of each given dose.

referred to above afforded an opportunity to examine the ergot alkaloids under conditions not hitherto employed (20). Figure 13 gives an example of the results obtained with dihydroergotamine methansulfonate. This ergot alkaloid exhibits antiaccelerator activity of the order of one three hundredth of that of veratramine. The antiaccelerator effect develops gradually, resembling the effect of veratrosine, and does not set in abruptly like the effect of veratramine.

5. *The use of antiaccelerator cardiac agents.* Substances with a selective an-

tagonistic effect upon the positive chronotropic action of the sympathomimetic amines would have therapeutic usefulness, provided their therapeutic range were adequate. We do not possess at present the requisite experimental evidence to assess the therapeutic range in man of any one of the antiaccelerator agents, except that the experiments in mammals suggest a very narrow range between effective antiaccelerator action and toxic action in the intact animal. In the first

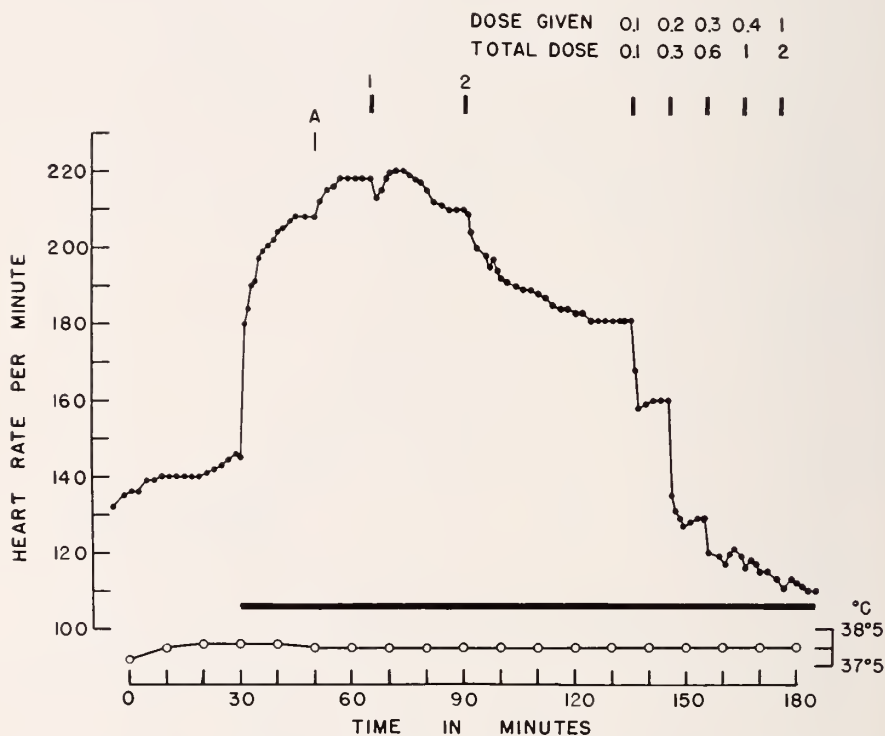


FIG. 13. *The antiaccelerator action of dihydroergotamine.* Dog, male, 11.5 kgm. Heart-lung preparation (May 25, 1951). Total blood volume 750 cc. Mean arterial pressure 89 mm. Hg. Systemic output approximately 500 cc. per minute. Temperature of the blood 37.7 to 38.1° C. Ordinate: Heart rate per minute. Abscissa: Time in minutes. Black bar: continuous infusion of 3 microgm. *l*-epinephrine base per minute. At A, 10 mgm. atropine sulfate was injected. At 1, 12 mgm. and at 2, 28 mgm., respectively, of dihydroergotamine methanesulfonate was injected. Starting at time 135 minutes, veratramine was administered in five doses at 10 minute intervals between successive doses. The top row of figures represents the doses in mgm. actually given. The figures below are the total doses administered up to and including the respective single doses. The maximal rate effect (heart rate 110) was achieved with the total supplemental dose of 2 mgm. veratramine.

publication on veratramine (1) its convulsant properties were discussed. In a later communication (17) it was clearly stated, that clinical use of veratramine was not possible on account of its toxicity which manifests itself in clonic convulsions. Nevertheless, an unwarranted and reckless use of veratramine in man has recently been made (21). Severe toxic reactions resulted, as might have been expected.

When a group of substances exhibits a high degree of selectivity of action, it

should attract the investigative curiosity of the pharmacologist. The search for selective activity and the analysis of its nature is the central theme of his scientific pursuit. The interest in antiaccelerator cardiac agents is heightened by the importance of the site of their selective action. It is at least probable that such substances will be useful tools in the elucidation of the mechanism by which the sympathomimetic amines, and accelerans stimulation, increase the rate of impulse generation in the automatic tissue of the heart.

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MODIFICATIONS OF THE HEART SOUNDS IN BUNDLE BRANCH BLOCK*

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It is a general belief that the electrocardiographic changes are the only objective findings in bundle branch block. However, nonsimultaneous excitations are followed by asynchronous contractions of the ventricles and the shifted timing of the electrical impulses is mirrored by the shifted timing of mechanical events. In bundle branch block, as well as in ventricular extrasystoles, mechanical asynchronism can be detected through observation of the arterial and venous tracings, the electrokymogram, and the phonocardiogram.

PREVIOUS STUDIES

Splitting of the heart sounds, attributed to ventricular asynchronism, was described by auscultation (1-4) and in tracings (5-8).

Well known textbooks of cardiology (9-16) and monographs on bundle branch block (17, 18), report this splitting as an accepted fact. However, a new graphic study of the problem was considered necessary before accepting these data.

METHODS

Twenty-four phonocardiograms of cases of complete bundle branch block were selected from the files of this Laboratory. Cases presenting murmurs, those having incomplete or imperfect records, and those with an incomplete block, were excluded. All cases presented ventricular asynchronism; this was evidenced by the electrocardiogram and in most cases also by mechanical tracings (jugular and carotid tracings, electrokymogram).

Nine cases had right bundle branch block, 15 had left bundle branch block. The patients were of both sexes, and ranged from 20 to 83 years of age.

All records were obtained with the Sanborn Stetho-Cardiette using first the stethoscopic and then the logarithmic microphone, according to the description of Rappaport and Sprague (19). However, measurements were made only in stethoscopic tracings because the low-pitched vibrations, an important part of the tracings, are poorly recorded by the logarithmic microphone.

The following electrocardiographic and phonocardiographic data were analyzed:

- (1) QRS duration and the time of the intrinsicoid deflection in the delayed side whenever the precordial leads were available.
- (2) Presence of an atrial sound and its amplitude in comparison with the first sound.
- (3) Configuration of the first sound and its amplitude in comparison with the second sound.
- (4) Duration of the central phase of the first sound (second and third part of the four comprising the first sound). This was measured and compared with the normal values found in a previous study by one of the authors with Mendoza and Alimurung (21). Since the am-

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plitude of the first sound in these cases was always below normal, only the central phase was measured in order to avoid incorrect values due to the particularly low amplitude of the initial and final parts of the sound.

(5) Configuration of the second sound.

RESULTS

The results are presented in table form.

Table I shows the data obtained in a group of 15 patients presenting *left bundle branch block*. *Splitting of the second sound was present in all cases but two* (cases 4 and 7) where this sound was prolonged (fig. 1). *The first sound was never split. Prolongation of the central phase of the first sound was found in all cases* (figs. 1, 2, 3). This seemed to be directly related with the prolongation of QRS and the delay of the intrinsicoid deflection in the left-sided pre-

TABLE I
Left bundle branch block

CASE NO. AND AGE	DURATION OF QRS	HEIGHT OF 4TH SOUND IN COMPARISON WITH 1ST SOUND	1ST SOUND AT APEX		SECOND SOUND
			Duration of central phase	Height in comparison with 2nd sound, same area	
1 48	0.12	—	0.081	Same	Split
2 74	0.16	—	0.12	3/4	Split
			(3 vibrations)		
3 67	0.12	1	0.11	1/2	Split
4 64	0.12	3/4	0.08	3/4	Prolonged
5 61	0.11	3/4	0.08	1 and 1/4	Split
6 73	0.12	1/4	0.09	3/4	Split
7 45	0.13	Same	0.09	Different in the various areas	Prolonged
8 41	0.12	3/4	0.08	Same	Split
9 45	0.14	—	0.11	2, 3	Split
10 69	0.16	—	0.09	Same	Split
			(3 vibrations)		
11 83	0.14	1/2	0.09	3/4	Split
12 63	0.13	1/2	0.11	1/2	Split
13 68	0.13	1/2	0.10	1/2	Split
14 74	0.13	—	0.10	Same	Split
15 69	0.13	—	0.12(?)	Almost absent	Split

cordial leads. In some patients (cases 2, 10) where the QRS interval was particularly prolonged, the first sound was not only prolonged but also presented three main groups of vibrations (fig. 5). In 11 out of 15 cases (73%), the amplitude of the first sound was reduced in comparison with that of the second at the same area (fig. 1).

A loud fourth (atrial) sound was found in 9 cases (60 per cent) (fig. 1). The height and the pitch of this sound were such that, according to the definition of Luisada and Roitman (22), there frequently was a pathological triple rhythm (old term: gallop rhythm).

Table II shows the data obtained in a group of 9 patients presenting *right bundle branch block*. *Splitting of the second sound was present in all tracings. The first sound was never split. Prolongation of the central phase of the first sound was present in all cases*. However, the electrocardiographic changes and the modifications of the first sound were less directly related than in left bundle branch block. In 5 out of 9 patients (55%), the amplitude of the first sound was between $\frac{1}{4}$ and $\frac{3}{4}$ of that of the second sound over the same area.

First Second
Fourth Sound Sound
Sound

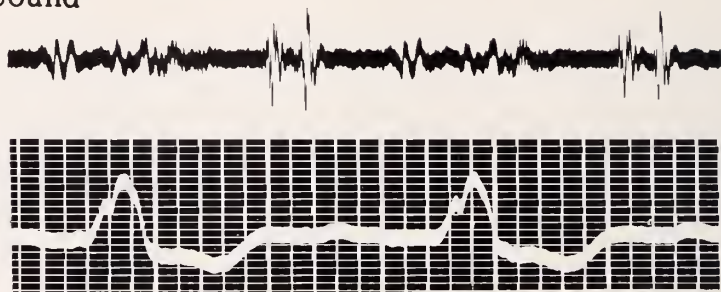


FIG. 1. Left bundle branch block. Loud 4th (atrial) sound; weak and prolonged first sound; faint systolic murmur; split second sound (stethoscopic microphone).

First Second
Sound Sound

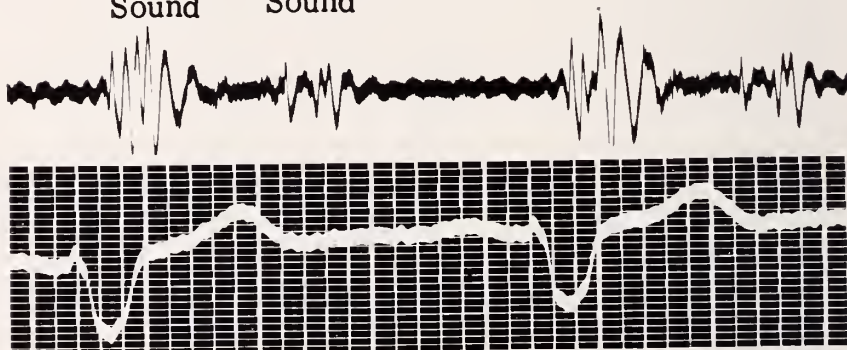


Fig. 2. Right bundle branch block. Distorted and prolonged first sound; split second sound (stethoscopic microphone).

First Second
Sound Sound

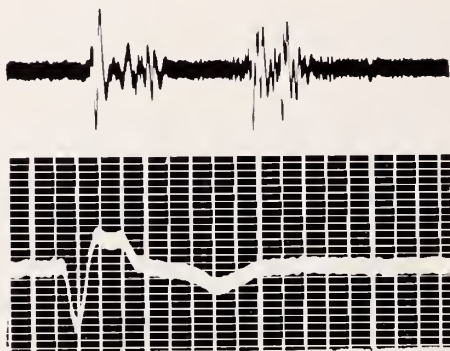


FIG. 3. Right bundle branch block. Prolonged central phase of first sound; split second sound.

A fourth (atrial) sound, was found in 4 cases (44 per cent). The height and the pitch of the additional sound were such that, according to Luisada and Roitman (22), there was a pathological triple rhythm.

DISCUSSION

Splitting of the second sound is an undeniable finding in many previously reported cases. On the other hand, splitting of the first heart sound cannot be accepted without careful examination of the technique used and of the documents presented in previous studies.

None of the above mentioned authors used the "stethoscopic" method of phonocardiography advocated by Rappaport and Sprague (20). The technical characteristics of most of the older instruments were such that the high-pitched vibrations were amplified to a greater extent. This was done empirically in order to obtain tracings which could be compared with data of clinical auscultation.

TABLE II
Right bundle branch block

CASE NO. AND AGE	DURATION OF QRS	HEIGHT OF 4TH SOUND IN COMPARISON WITH 1ST SOUND	1ST SOUND AT APEX		SECOND SOUND
			Duration of central phase	Height in comparison with 2nd sound, same area	
1 67	0.14	—	0.12	3/4	Split
2 20	0.13	—	0.09	1 and 1/2	Split
3 60	0.12	3/4	0.12	1/4	Split
4 60	0.13	1/4	0.10	3/4	Split
5 55	0.12	—	0.08	Same	Split
6 61	0.12	—	0.11	Same	Split
7 80	0.12	Same	0.10	1/2	Split
8 75	0.14	Same	0.12	2	Split
9 43	0.12	—	0.09	3/4	Split

Thus, the low-pitched vibrations, which are an important part of the first sound, were poorly recorded or not at all. It should be noted that two groups of higher and higher pitched vibrations are frequently visible within the first sound complex (22, 14, 20, 23). They correspond to the two main valvular events, e.g. closure of the a-v valves and opening of the semilunar valves (fig. 4). If the tracing is recorded with the stethoscopic microphone, these two groups may appear connected by smaller and lower-pitched vibrations. If, on the contrary, it is recorded by means of the logarithmic microphone (or any other microphone which fails to record proportionately the lower pitched vibrations) the two groups may appear as distinct and separated.

One can differentiate a pathologically split first sound from a normal first sound with clear division of the two phases as follows: the duration of the central phase of high vibrations of the first sound is measured and is compared with the average and maximal figures for normal subjects (20).

It was considered useful to analyze the tracings published by the above mentioned authors, and whenever possible, measure the duration of the central

phase in their tracings. All reproduced tracings were recorded with the conventional film speed of 25 mm. per second. This does not allow sufficient spreading of the vibrations and makes exact measurements difficult. Moreover, whenever the first sound had an unusual configuration, the vibrations of a short systolic murmur may have prolonged the sound. In all the published illustrations (except fig. 6 B of Wolferth and Margolies (5) and figure 33 of Benchimol (18)) the total duration of the first sound seems to be within the extreme physiological limits. It should be noted that, in tracings published by the various authors with older phonocardiographs, the central phase of the first sound should be shorter than in those studied by Luisada and coworkers (21) with the stethoscopic method. Figure 6 emphasizes the misleading properties of inadequate methods of recording: a loud snap in early systole simulates splitting of the first sound in the logarithmic tracing of a case with dilated aorta and no bundle block.

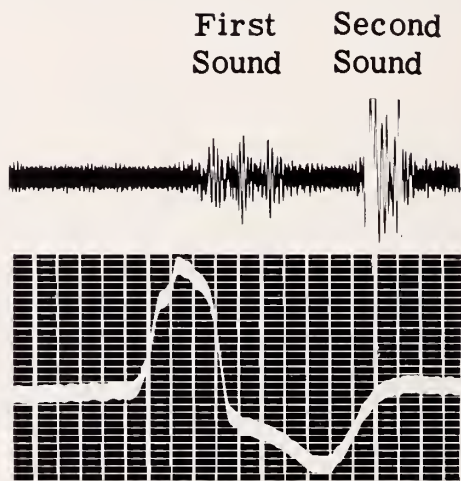


FIG. 4. Normal subject. Simulation of splitting of the heart sounds. Loud opening sound of the mitral valve (os). (Stethoscopic microphone).
(from Luisada, Mendoza, and Alimurung)

Another observation which should be made is that, in several of the published tracings, only the first sound is called "split", while the second is normal. A ventricular asynchronism cannot fail to show splitting of the shorter second sound, when the first sound is split.

In summary, a careful scrutiny of the cases previously published fails to reveal conclusive evidence of pathological splitting of the first sound.

In all our cases, except two, the second sound was split. The exceptions were represented, however, by patients having severe prolongation of the second sound. Splitting of the second sound is due to asynchronous closure of the semilunar valves. Whenever cor pulmonale and mitral stenosis are excluded and the electrocardiogram indicates bundle branch, this asynchronism can be explained only by a delay in the contraction of one of the ventricles. It is further confirmed by correlation of the sound tracing with the carotid tracing.

In 73 per cent of patients with left bundle branch block and in 55 per cent of patients with right bundle branch block *the first sound presented vibrations of low amplitude*. This could not be explained by a longer interval between atrial and ventricular contraction as postulated by Levine and Harvey (10) because it occurred also in cases having a normal P-R interval.

A possible, though not completely satisfactory explanation, is the following: the 1st sound is caused by vibrations arising in both ventricles; if the contractions of the two chambers are not simultaneous, a spreading of the vibrations and a lower intensity may be expected.

The duration of the central phase of large vibrations was found prolonged in all cases with either left or right bundle branch block if compared with the

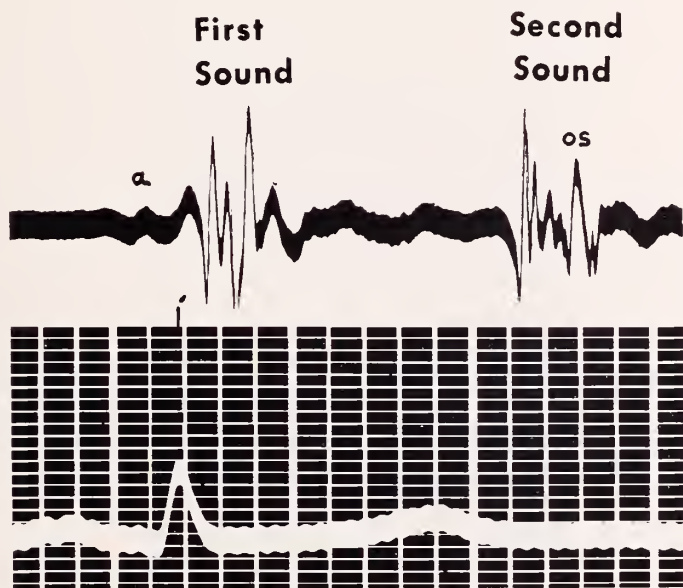


FIG. 5. Left bundle branch block. Division of the first sound in three parts; splitting of the second sound (logarithmic microphone).

average duration of that phase in normal subjects of equivalent age. While a direct relationship between duration of QRS and duration of the central phase of the first sound was found in left bundle branch block, this relationship was less close in right bundle branch block.

As already stated, the first sound complex may present two main groups of vibrations, one coinciding with the closing of the a-v valves; the other with the opening of the semilunar valves (21). The interval between these two groups is about 0.05 (20) and is equivalent to the isometric tension periods of the two ventricles which also lasts about 0.05 sec. in man (Wiggers (25)).

In bundle branch block, the interval separating the contractions of the two ventricles is determined by the time interval necessary for the stimulus to reach the opposite branch through the interventricular septum. This time interval,

according to Sodi-Pallares *et al.* (27) corresponds to about 0.04 second. Longer intervals seem to be caused by addition of other causes of delay in the contraction of one ventricle (hypertrophy, intraventricular disturbance of conduction).

It is apparent that, in pure bundle branch block, a delay of 0.04 is too short to cause dissociation of a sound complex having a central phase of 0.06 to 0.08 and two groups of vibrations separated by an interval of 0.04. On the other hand, the second sound, having only a brief central phase of large vibrations, is easily split whenever there is delay in the contractions of the two ventricles.

If the delay between the contractions of the two ventricles reaches 0.05 sec., this time interval becomes equivalent to the duration of the isometric tension

TABLE III

Effect of hypertension or unilateral conduction disturbance on the heart sounds in left bundle branch block

	1ST PHASE OF 1ST SOUND	2ND PHASE OF 1ST SOUND	SECOND SOUND
Hypertension of greater circulation	Unchanged	Left ventricular component further delayed	Aortic component relatively anticipated
Hypertension of lesser circulation	Unchanged	Right ventricular component relatively delayed	Pulmonic component anticipated
Delayed conduction of left ventricle	Further delay of left ventricular component	Further delay of left ventricular component	Further delay of aortic component
Delayed conduction of right ventricle	Relative delay of right ventricular component	Relative delay of right ventricular component	Relative delay of pulmonic component

period. Then, closure of the a-v valves of the delayed ventricle takes place during the opening of the semilunar valves of the normal ventricle. This leads to formation of three groups of vibrations within the first sound-complex; the central phase is the loudest because it is due to summation of vibrations arising in both ventricles (fig. 4). This type of first sound was described by Braun Menendez and Orias (23) and was present in one tracing of Wolferth and Margolies (5). It was present in three of our cases of left bundle branch block.

The dynamics of valvular opening and closing become more complex whenever bundle branch block is complicated by hypertension, unilateral conduction disturbance, or both (Schwedel and coworkers (26)). Hypertension of the greater circulation increases the duration of the tension period of the left ventricle by delaying the second part of the first sound. On the other hand, it accelerates the closure of the aortic valve. The effect of the above disturbances is described in table III which considers only left bundle branch block. This explains how systemic hypertension may accentuate the prolongation of the first sound and

neutralize the splitting of the second sound in left bundle block. On the contrary, systemic hypertension may decrease the prolongation of the first sound and increase the interval between the phases of a split second sound in right bundle branch block. The opposite would occur in cases where chronic hypertension of the lesser circulation complicates bundle branch block.

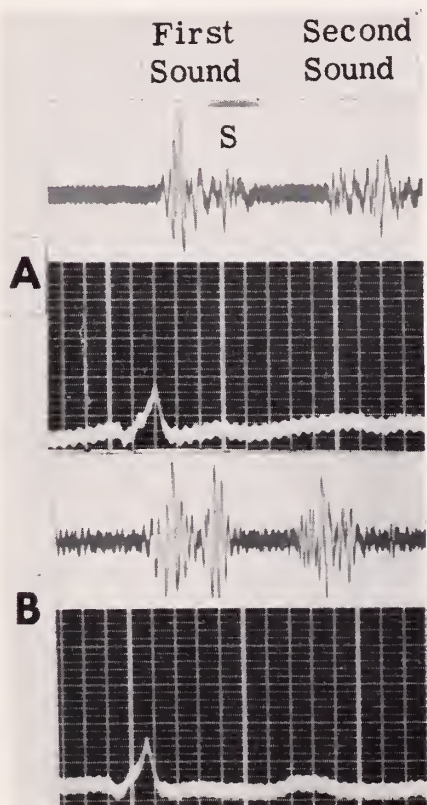


FIG. 6. Simulation of split first sound (only in the logarithmic tracing) by an aortic snap (S) in a case with dilation of the aorta and normal QRS duration. Compare this tracing with that of fig. 3.

SUMMARY

1. A phonocardiographic study is made of 24 cases of complete bundle branch block.
2. The second heart sound was split in 22 cases and prolonged in the other 2, as a result of ventricular asynchronism.
3. The first heart sound was prolonged in all cases; it was of poor amplitude in 73 per cent of cases of left bundle branch block and in 55 per cent of cases of right bundle branch block.
4. In none of the observed cases was there a splitting of the first sound. On the other hand, a division of this sound into three groups of vibrations was observed in two cases with left bundle branch block and intraventricular block.

5. The mechanism of production of the first second is discussed and the theoretical impossibility of its splitting by effect of bundle branch block is stressed.

6. The possible influence of additional ventricular lesions (i.e. blocks, hypertrophy) or hypertension in one of the great vascular systems on the changes of the heart sounds, is further discussed.

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THE TRANSFER OF DRUGS INTO THE MILK*

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The transfer of drugs into the milk is an interesting problem theoretically as well as from a practical, pediatric point of view.

It is generally accepted that most of the vitamins are transferred to the milk. Correct observations were made even before our knowledge about the vitamins developed. Takassu (28) described Beriberi in children fed the milk of their beriberi-sick mothers, who could be protected by any other food. At this time, of course, this seemed to demonstrate the presence of a poison in the milk of the sick mother.

Ingested fat reaches the milk unchanged (Engel,(6)) the constituents of milk-fat is altered according to the food ingested. It was thought for a long time that fat soluble substances only were secreted in the milk.

The first observers described the fact that most drugs appear in the milk in traces only. Thiemich (30) claimed that iodine, bromine, salicylic acid appear in the milk in measurable amounts, but mercury in traces only. Bucura (3) found the following substances in the milk: iodine, bromine, salicylic acid, anti-pyrine, arsenic but no cathartics. Joachimowits (15), Bucura's pupil in Gynecology and E. P. Pick's in Pharmacology, extended these experiments and found with a better technique also traces of many cathartics. Kwitt and Hatcher (16) found bromine and traces of morphine, of iodine, but not phenolphthalein, codeine, barbiturates or salicylates. Thyson (32) and coworkers reexamined this field and found traces of phenolphthalein, calomel, senna and rhubarb, but not enough to cause any symptoms in the nurslings.

Gramèn examined the passage of ether in anesthesia into the milk and found always the same level in blood and milk. However, substances which are taken by the mother for a prolonged time are of greater importance. Alcohol may be found in the milk, but the highest level which Frontali (8) could obtain was 0.56% of alcohol in the milk.

Very often the transfer of alkaloids was examined, but always traces only found. Morphine was of special interest as nurslings tolerate morphine quite poorly. We find in the older literature some descriptions of morphine poisoning by means of breast feeding of the addict mother. Thiemich quoted an observation of the death of a child from morphine in the mother's milk, but the dose taken by the mother was high enough to cause convulsions and was probably extremely high. No reports about morphine poisoning of nurslings have been reported in the last decades. On the contrary, Menninger-Lerchenthal (17), Hatcher (13), Perlstein (21) described a disease of the newborn children of addict mothers with convulsions and vomiting, which is improved by morphine and is explained as withdrawal symptoms because of the passage of morphine

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through the placenta and the lack of morphine in the milk. Perlstein (21) who speaks about congenital morphinism, was able to cure the children by sedation with phenobarbital.

Nicotine in the milk of mothers who smoked heavily was examined by Thompson (31), Hatcher and Crosby (13), Emanuel (5), Perlman (20) and others. It was mostly claimed that milk production is impaired, but that the amount of nicotine in the milk remains very low. Emanuel found 1-8 hours after the smoking of 7-15 cigarets only 0.005 mgms of nicotine per liter of milk. Nevertheless he discusses the possibility of increased tolerance of these children, but the amounts of nicotine remain probably always under the toxic level.

It was hoped with the development of the antibiotics, that it will become possible to treat nurslings by injections given to the mother. The amounts with all antibiotics secreted in the milk is always much too small for such purposes. Firstly hexamethylenetetramin was examined. Hald (12) was the first to find traces of urotropin in the milk. The result was confirmed by Rieder (24) and Usener (33). Usener found that the relationship of urotropin in the urine and in the milk was never higher than 3 or 4 to 1. A disappointment was also met with salvarsan. Baisch (2), Caffarena (4), Stewart and Pratt (27) found only traces of salvarsan in the milk. Oppenheim (9), described even new skin eruptions of the nurslings during the treatment of the sucking mother. Also the sulfa-drugs appear in traces only in the milk (Adair (1) and co-workers, Hepburn (14) and co-workers and many others). The same is true with penicillin (Seeley (25) and co-workers). Rozansky and Brzesinsky (26) found 10-15% of the blood level in the milk two hours after the injection. Greene (11) and co-workers found 0.015-0.06 units of penicillin in one cc. of the milk, following the injection of 100,000 units to the mother.

Barbiturates are excreted in the milk in small amounts (Freunddorf (7), Thyson (32) and others). Here we find the complication that the newborn is extremely sensitive to these drugs. The barbiturates are "hypothalamic" hypnotics, according to the classification of E. P. Pick (22). We (18) have stressed the fact that drugs acting on the cortex, which is underdeveloped in the newborn act weakly whereas the hypothalamic centers lack the inhibition of the cortex, and drugs have here an especially strong effect. The examinations of Thyson have shown that phenobarbital is often excreted in the milk and the children show definitively the hypnotic effects. Unfortunately exact quantitative examinations are impossible as we cannot eat the cake and have it too. We cannot examine the milk which is fed to the child.

We see that most drugs are secreted in the milk in negligible amounts only. But since the first experiments of Thiemich's bromine was often found in relatively high amounts in the milk. Bromine is distributed in the body together with chlorine and reaches in this way all cells of the body. It is probably this mechanism which explains the appearance of bromine and iodine in the milk. Van der Bogart (34) has even described a nursling with bromine acne who received his bromine only from the mother's milk. Thiouracil is another drug which appears in the milk in high amounts. Williams (35), Goldschmidt (9)

and others have claimed this fact. Williams found it always higher in the milk than in any other body fluid. The blood level in one patient was one mgm%, but in the milk 12 mgm%, in another patient in the blood 3.2 mgm%, and in the milk 9 mgm%. The mechanism of this transfer is not understood but would be worthwhile examining in detail.

SUMMARY

Most drugs appear in the milk in traces only and are, therefore, quite harmless for the nursing. A few drugs, such as the barbiturates, may have some effect on the child since the newborn is especially sensitive to them. But most of the drugs appear in the milk in much smaller amounts than in the blood. Bromide (maybe also iodide) are found in blood and urine in the same level and are therefore not harmless for the child. Thiouracil is the only substance found up to this time, which appears in the milk in higher level than in blood or urine.

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EFFECT OF EXCESSIVE DOSES OF CORTISONE, ACTH AND PROLACTIN IN PREGNANT AND NURSING MICE*

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The effects of excessive doses of cortisone† in pregnant mice have been previously reported. The outstanding features were the widespread distribution of the mammary tissue and its engorgement with milk in the mother, and the retardation of development and death of the progeny in utero or early post partem life. When two subcutaneous injections of 2.5 mgm. of cortisone were given seven to eight days before parturition the feti died in utero and showed signs of retarded development and often autolysis. When 2.5 mgm. cortisone was administered in the last three to five days of pregnancy the offsprings were born dead or died shortly after birth; when injected two days before parturition the babies were born alive but died within two to five days (1).

A similar deleterious effect of large doses of cortisone on the feti has been observed by Courrier and Collonge (2) in rabbits and in mice by Robson and Sharaf (3). There are also reports of production of congenital defects in the offspring of pregnant mice treated with cortisone (4).

Excessive doses of cortisone were not only harmful to the offspring when given to the mother during pregnancy but also when injected to the nursing mother shortly after parturition. Three daily doses of 2.5 mgm. of cortisone starting one to three days after delivery had a lethal effect on the litter. The babies lost weight, appeared dehydrated and died within three to five days. At autopsy the constant findings were small interscapular hibernating fat bodies (these fat bodies are very large in newborns and very young offsprings) small thymus and absence of milk in the stomach. This latter finding is important to note, since the mother, when sacrificed, showed abundance of mammary tissue engorged with milk which exuded freely when the breast tissue was cut. The investigation of the effect of cortisone in pregnancy and on suckling were further extended to include the influence of excessive doses of cortisone on the offspring when the nursing mother is treated with cortisone eight to twelve days after parturition, the effect of smaller doses of cortisone on pregnancy and the survival, development and upbringing of offspring. Experiments with prolactin and ACTH were also performed.

METHOD

The experiments were performed on sixty Paris R III mice. The cortisone was administered daily in doses of 2.5 mgm., 0.25 mgm., or 0.05 mgm. suspended in 0.1 cc. cortisone vehicle. The dose of prolactin‡ was 1 mgm. (equivalent to

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† Cortone—Merck.

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20-25 units) dissolved in 0.1 cc. NaCl. ACTH was administered in 2.5 mgm. doses dissolved in 0.3 cc. NaCl and were injected daily in three divided doses. All injections were given subcutaneously on the back. Pregnant non-treated mice served as controls. Cortisone vehicle was not used as it had been shown to have no effect on offspring or mammary tissue of the mother (1).

RESULTS

Effect of Excessive Cortisone Doses. To a group of mice 2.5 mgm. of cortisone were given on four successive days starting on the eighth to twelfth day after parturition. Figure 1 represents the typical growth curve of a "control litter" (litter from an untreated mother) as compared with the "cortisone litter" (litter from the cortisone treated mother). The treatment of the mother started on the tenth day after parturition and was given for four days. As can be seen the growth

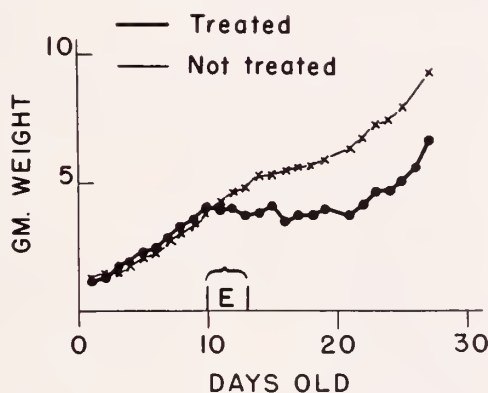


FIG. 1

curves of both control and "cortisone litter" are identical until the start of the treatment of the mother. Twenty-four hours after the first cortisone injection to the mother, the "cortisone litter" fails to show gain of weight, and the curve remains flat during the treatment of the mother and persists until the twenty-first day of age when the curve begins to rise. The "control litter" continues to grow but at a slower rate between the sixteenth and twenty-first day of age and again at a faster rate after the twenty-first day. This change in rate of growth is apparently due to weaning which ordinarily takes place at this time. The "cortisone litter" also start to grow after the twenty-first day of age but is still smaller than the control on the twenty-seventh day of age. Each curve in this figure represents the average weight of one litter of males and females combined. If the growth of litters is followed for more than twenty-eight days of age average curves must be calculated separately for males and females, since males grow faster than females from this date on.

Figure 2 shows the growth of litter mates from the twentieth day until the fiftieth day of age. *A* represents the litter mates of three "control litters," *B* of three "cortisone litters." The mothers of the "cortisone litters" were treated

with 2.5 mgm. of cortisone on four successive days starting nine to twelve days after parturition. Fig. 2 indicates that the males of the control litter grow faster than the females from the twenty-sixth to the twenty-eighth day on, while in the "cortisone litters" this difference in growth of males and females appears about the fortieth day. In addition, there can also be seen a delay in growth of male and female when compared with the growth curves of control litters. Another feature in the "cortisone litter" was the sparseness of hair, especially in the first six weeks. At the age of three months the animals appeared normal, had about the same weight as the controls, were able to mate and produce normal offspring.



FIG. 2

Effect of 0.05 and 0.25 mgm. of cortisone. Twelve pregnant mice were used. Six mice received daily injections of 0.05 mgm. cortisone starting seven, five and two days respectively before parturition. Six mice were treated similarly with 0.25 mgm. of cortisone. All twelve mice delivered normal litters. In three mice of each group the injections were continued until weaning. All the babies were raised. Their growth during the suckling period was about the same as in the control litter, but a difference in growth rate of male and female did not begin until about the fortieth day of age. To the other three mothers of each group cortisone administration was continued for two to three days after parturition. The animals were sacrificed, and the mammary tissue examined. The breast tissue of the mice treated with 0.05 mgm. of cortisone was thick and had a yellow appearance; with 0.25 mgm. the mammary tissue was widespread and dotted with white spots.

Experiments with ACTH. As had been previously reported large doses of ACTH (2.5 mgm. daily) administered before parturition and continued until weaning did not interfere with the delivery of live litters nor with rearing of the babies. Also in these litters as in those from mothers treated with 0.05 mgm. of cortisone, no effect on the growth curves until weaning is seen and sex differences in growth rate started about the fortieth day.

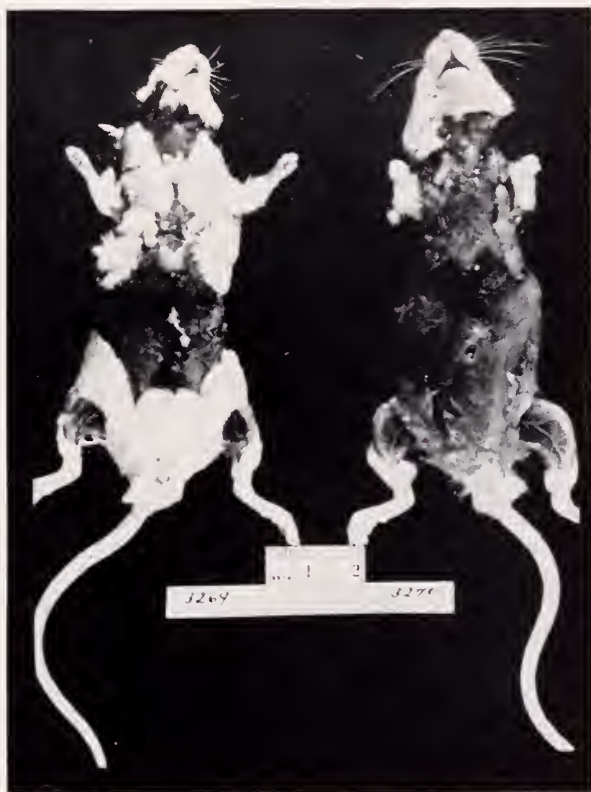


FIG. 3. Breast tissue in cortisone treated (A) and control (B) pregnant mice

Figure 3 shows the spread of breast tissue of two mice killed one day after parturition. A was treated daily with 2.5 mgm. cortisone for four days before parturition and B had no treatment. As can be seen there is a striking difference in the appearance of the cortisone and non treated mouse. Two pregnant mice treated with 2.5 mgm. of ACTH daily for four days before parturition and sacrificed after parturition showed the same spread of breast as the untreated mouse. In the ACTH treated mice large adrenals were present; in the cortisone treated mice the adrenals were small. The effect of the two hormones administered simultaneously three to four days before parturition on the litter and the maternal breast tissue was the same as observed with cortisone alone, but the adrenals were enlarged as in ACTH treated mice. A similar effect of ACTH on adrenal

cortex atrophy caused by adrenocortical extract was observed by Ingles when large doses of cortical extract were given simultaneously with ACTH (5).

The effect of cortisone with its striking mammary reaction in pregnant and in nursing mice was compared with the effect of prolactin which increases the output of milk in nursing mothers. Prolactin was injected on four successive days to the nursing mother two to three days after parturition. Twenty-four hours after the last injection the mother was removed from the litter and sacrificed. The breast tissue was thickened and yellow in appearance. When the same experiment was repeated and the mother killed twenty-four hours after having



FIG. 4. Offspring from a cortisone-prolactin (A) and prolactin (B) treated mothers.

been separated from the sucklings, the breast tissue was thick, white and engorged with milk which exuded freely when the tissue was cut. Daily injections of prolactin, three to four days before and after parturition did not interfere with the delivery of a normal litter nor with the nursing of the offspring. Prolactin, given simultaneously with 2.5 mg. of cortisone before parturition results in death of the offspring and exaggerated engorgement of the mother breast. One mouse which gave birth to eight babies was treated with prolactin and cortisone simultaneously for three days starting immediately after delivery. Another mother with seven newborn babies received prolactin for three days. The litter of the prolactin-cortisone treated mother lost weight and died within five days. The average weight at death was 1.1 Gm. The litter of the prolactin-treated mice

thrived, gained weight, and the average weight on the fifth day was 4.1 grams. Fig. 4 shows a difference in size and appearance of "prolactin-cortisone" and of "prolactin" offspring. This picture was taken five days after birth. The prolactin-cortisone treated mother was killed. The breast tissue was tremendously congested with milk. Although the mother was constantly attending to the litter, and the babies were hanging on to the nipples, no milk apparently was delivered to the sucklings. This suggests that the ejection or "let-down" of milk was impeded. Ely and Peterson (6) advanced the idea that the "let-down" of milk was caused by the oxytocic principle of the pituitary. Two preliminary experiments to increase the ejection of milk with pitocin in mice treated with cortisone immediately after parturition were not successful. Further studies on this subject are in progress.

The ejection of milk does not seem to be greatly impaired in nursing mice treated with 2.5 mgm. of cortisone nine to twelve days after parturition. The babies from these cortisone-treated mothers killed after the third or fourth cortisone injection showed milk in the stomach. Whether the arrest of growth is due to a change in the composition of the milk or to transmission of cortisone by the milk to the sucklings or both factors is not clear. The retardation of growth and the sparseness of hair seems to speak, at least in part, for transmission of cortisone with the milk, since the same symptoms can be produced in infant mice (7) and in infant rats (8).

The histology of breast tissue from cortisone, prolactin and prolactin plus cortisone treated mice were studied by Dr. William Antopol. The findings were as follows:—(Hematoxylin eosin stains on paraffin sections)

Breast tissue from pregnant mice treated with 2.5 mgm. cortisone on four successive days: The acini are markedly distended with a pink staining secretion which is honeycombed with vacuoles from which fat had been dissolved. The lining cells are flattened, the cytoplasm is inconspicuous, thin and elongated, and the nuclei compressed and flat. The acini abut against each other so that comparatively little intervening tissue is seen.

Breast tissue from pregnant mice treated with 1 mg. prolactin on four successive days: The acini are small in comparison with those from the cortisone treated mice. The lining cells are cuboidal. Within the cytoplasm of these cells are large conspicuous vacuoles from which fat has been dissolved. The nuclei are usually round and basal in location. Loose areolar tissue containing monocytic cells is irregularly dispersed between the acini. Some of the acini contain little secretion while most are filled. The secretion when present is more basophilic and granular, less homogeneous, and contains fewer and smaller fat droplets than in the cortisone treated mice.

Breast tissue from pregnant mice treated with 2.5 mg. cortisone for four days simultaneously with 1 mgm. prolactin: The secretion is similar to that in the breast from the E treated mother, except that it is slightly less abundant and more basophilic and the fat droplets are irregular and larger. The acinar distension is not as striking. The cells lining the acini are low cuboidal and contain fat vacuoles. The nuclei are round and only slightly compressed.

SUMMARY

1) 2.5 mgm. of cortisone administered to nursing mice nine to twelve days after parturition (a) retards the growth of the offspring, (b) produces sparseness of the hair, (c) the male does not show a greater growth rate than the female until forty days of age. Normally the male grow faster than the female from the twenty-eighth day of age.

2) Daily injection of 0.05 mgm. cortisone, 0.25 mgm. cortisone, or 2.5 mgm. ACTH administered seven, five or two days before parturition and continued until weaning had no significant effect on the offspring except for a delay in the sex difference in growth rate until the fortieth day of age.

3) Four injections of 2.5 mgm. ACTH have no effect on the maternal breast tissue.

4) Large doses of ACTH given simultaneously with large doses of cortisone do not counteract the lethal effect before parturition, of cortisone on the offspring nor do they inhibit the maternal breast change, but they do counteract adrenal atrophy caused by cortisone.

5) Large doses of prolactin do not have the cortisone effect on the maternal breast tissue.

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THE CHANGING PATTERN OF INFECTIOUS PROCESSES UNDER THE INFLUENCE OF CORTISONE*

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The writing of this paper brings back memories of the year 1932, a good part of which was spent at the Pharmacological Institute of the University of Vienna. During that period I had the honor and good fortune to be closely associated with Professor Pick as both pupil and friend. There is no doubt that I learned a great deal of pharmacology and experimental therapeutics. More important however was the opportunity afforded me to observe the greatness and unselfishness of so exemplary a person. Professor Pick gave "all" to his students, and took more personal pride in their progress than he did in his own work. Those months spent with him were productive ones and have proven of inestimable value to me not only in scientific knowledge but also in human understanding. (W. A.)

It was originally intended to limit the subject of this paper to the effects of cortisone on infectious processes. However, the clinical reports for both ACTH and cortisone are very much alike and in many instances ACTH and cortisone effects are included without differentiation. Therefore it was felt that the inclusion of some of the ACTH findings with data on cortisone would be of value. There is no doubt that cortisone and ACTH effects are not identical. The observations of atrophy of the anterior pituitary, adrenal cortex and thyroid after cortisone administration and the enlargement of the adrenal cortex after ACTH indicate possible differences in physiologic effect. The fact that the adrenal cortical cells which atrophy under the influence of cortisone produce other substances besides cortisone, and that the cortisone producing cells which are stimulated by ACTH in turn also produce other substances in addition to cortisone, is sufficient cause for differences in effect seen with these hormones. In addition, cortisone acts on the inner portion of the adrenal cortex while ACTH stimulates the entire cortex. One must also consider that the effects of cortisone are related to the dose, no matter how great, while with ACTH the cortisone producing cells are stimulated and beyond a certain limit there is exhaustion of response without further cortisone output. Because of this latter effect, comparisons of cortisone and ACTH particularly with large doses, are not entirely valid. The complexity of the problem is made even greater when it is considered that accessory physiologic substances produced simultaneously may be either stimulatory or inhibitory. However, in most instances insofar as infections are concerned, particularly clinical infections in which a moderate dosage of cortisone and ACTH is employed, the effects are essentially alike. Because of this, we have extended the scope of this paper to include, to some extent, ACTH observations.

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The frequency of intercurrent infections which become evident during the use of cortisone is a source of great concern. That such infections would occur was not wholly unexpected since in the early period of the "cortisone era" unfolded by Hench, Kendall and colleagues (1, 2), it was reported that a high percentage of mice receiving large doses of cortisone developed "spontaneous" infections (3). Control animals which did not receive cortisone, did not contract these infections even when placed in the same cage under normal non-stress conditions with cortisone-treated animals that developed infections. It was concluded that the frequency of infection was due to a cortisone-mediated exhaustion of protective mechanisms with depletion of immune bodies, so that there was insufficient antibody to fix the antigen (3).

The human counterpart of this physiopathologic state in the experimental animal has been consistently reported. In the cases of Hench *et al.* (4), one patient developed a thrombophlebitis after cortisone, in another an existing acne was aggravated, and a third developed a gluteal abscess after a few days of ACTH. In this paper it is stated that "the use of these hormones in cases of tuberculosis should be investigated with caution. Studies now being made in animals by our colleagues in the Division of Experimental Medicine suggest that cortisone may neutralize the beneficial effects of streptomycin, retard fibrosis and reverse positive tuberculin reaction in experimental tuberculosis of guinea pigs" (5). One case of Hodgkin's disease with amyloidosis, reported by Beck *et al.* (6), developed an upper respiratory infection with mild cough after eighteen days of ACTH therapy. On the 20th day the patient developed abdominal complaints. The patient died and at autopsy an acute bronchopneumonia and an acute pneumococcal peritonitis were found. Boland and Headley (7) reported that acne of the face, shoulders, buttocks and legs appeared in one woman after fifty-one days of cortisone therapy. They considered this part of an androgenic effect. Soffer, Levitt and Baehr (8) described a case of lupus erythematosus which died of a pulmonary fungus infection developing during cortisone therapy. In the cases of Carey *et al.* (9) bronchopneumonia occurred in one patient on the third day of ACTH therapy and only responded to penicillin after ACTH was discontinued. Another case was complicated by a *Staphylococcus* septicemia, and still another developed an empyema necessitatis on the eighth day of treatment. This last patient died. Acne appeared in 6 cases of the group. Hench *et al.* (10) reported two cases with acneform eruption or folliculitis in a group of cases receiving ACTH. Pearson and Eliel (11) reported eight cases of chronic lymphatic leukemia receiving cortisone or ACTH, one of which died of an intercurrent infection (the type is not given). These authors commented, "prolonged administration of pituitary adrenocorticotrophic hormone or cortisone acetate may impair the localization and resolution of pyogenic infections. Administration of either of the hormones should not be continued in the presence of infections which fail to respond rapidly to specific therapy". We have recorded a case of Hodgkin's disease (12) receiving 2675 mg. cortisone in 25 days with death due to a disseminated fungus disease produced by an organism morphologically resembling penicillium. No cultural studies were made. More recently

a second case of Hodgkin's disease was seen by us which died of a diffuse bronchopneumonia produced by a fungus morphologically identical with that in the first case. Culture of this mold revealed it to be *Aspergillus niger*. This patient had received both cortisone and ACTH. A pneumonic fatality of an overwhelming lobular *Pneumococcus IX* pneumonia involving all five lobes of the lung was related by Bunim (13). Armstrong and Irons (14) reported, "During the last year at the Presbyterian Hospital we have seen instances, often at the autopsy table, of serious bacterial infections (suppurative pericarditis, sinusitis, cortical renal abscesses) which were clinically unsuspected in patients under treatment for the suppression of inflammatory phenomena in organs other than those in which the infection was found. This masking of the usual clinical signs of acute inflammation, e.g., fever, redness, tenderness and pain, thus provides a serious problem in the diagnosis of abdominal pain in patients under systemic therapy with ACTH and cortisone". Kirsner and Palmer (15) used ACTH in chronic ulcerative colitis. In this series "furunculosis of the arm in one patient responded less promptly to penicillin during the administration of corticotropin than after the hormone was discontinued. An infected toe in another man healed more slowly than usual. An extensive abscess developed in the buttocks of a third." In addition, pneumonia developed in one patient, and 23 of 38 patients developed acne. One case of peritonitis, recognized after ACTH therapy was instituted, had a progression "completely unaffected by extensive antibiotic and supportive treatment."

These apparently "spontaneous" or complicating infections correspond to the occurrence of spontaneous infection in mice receiving large doses of cortisone. It is interesting in this regard to consider a brief history of the organism *Corynebacterium pseudotuberculosis murium*, which could be cultured from the infections in cortisone treated mice. The organism was first described by Kutscher (16) and is now called *Corynebacterium kutscheri*. Seven years later Bongert (17) described the pathology of the disease and demonstrated its specificity for mice. In 1950 Wolf (18) reproduced the disease in mice which received 0.05 cc. of a suspension of *C. kutscheri* containing 200,000 organisms per cc. He reported the pathology to agree with that seen in cases of spontaneous infection. Here, as in our experience, uninfected animals in the same cage with diseased fellows did not contract the disease, and when untreated mice on a "Sunday devoured a comrade that had died of pseudotuberculosis, this cannibalism did not lead to disastrous results." Prior to this Polak (19) was able to reproduce this disease in mice by feeding large amounts of the organisms mixed with food. Wolf felt that since Polak made his observations in 1942 and 1943, during a period of general food scarcity, the mice were in all likelihood suffering from malnutrition. Wolf (20) further reported that *C. kutscheri* could cause the disease in mice previously infected with *Salmonella enteritidis*. In cortisone treated mice we also encountered "spontaneous" infections in association with *S. enteritidis* (12). All of the foregoing indicates that cortisone, as well as stress, lowers resistance and predisposes to infection. Since mice under the influence of cortisone demonstrate changes which in many respects are similar to those which appear after

administering alarm producing agents (Selye), it was postulated that cortisone is a hormone capable of eliciting an alarm reaction without the intermediary of the pituitary or the adrenal cortex (3). Similar observations to those found in mice have been made in rats, but the responsible "non-pathogenic" organism has not been identified (21, 22, 23).

To this point we have been considering the appearance of "spontaneous" infections, which at least were not clinically evident prior to the administration of cortisone or ACTH. Whether the organisms were present in a dormant reservoir or had already infected the subject with a clinically latent infection is not within the scope of this communication. In some instances evidence of the infection may be manifest only in a histologic subclinical form, while in other subjects under the influence of stress (or cortisone) the animal becomes susceptible to a simple symbiotic organism which is ordinarily nonpathogenic.

Since cortisone can produce the changes due to stress, the administration of cortisone or ACTH could be expected to produce considerable change in infectious processes present prior to cortisone and ACTH therapy. It has been shown repeatedly that cortisone modifies the inflammatory reaction (24, 25, 26) and also the reaction to bacteria (3, 12, 13, 21-23, 27-30, 33, 42, 45-47). In view of this it is not entirely unexpected that the administration of cortisone or ACTH modifies an existing infection, or an infection arising during the course of cortisone or ACTH therapy.

The influence of cortisone and ACTH on infections has been amply demonstrated in the experimental animal. Kuzell and Mankle (27) found that rats infected intra-articularly with *L*₄ pleuropneumonia organism were sicker after cortisone or ACTH treatment than untreated controls. Hart and Rees (21) produced a chronic tuberculous infection in mice. When cortisone was given nine weeks after infection the control mice remained fit, gained weight and none died. Eight out of eleven cortisone treated mice died within twenty-two days. The lesions in the cortisone treated mice were larger, and showed much more extensive necrosis and a great number of tubercle bacilli. Some of these mice developed infections due to unidentified organisms other than *M. tuberculosis*. Spain and Molomut (28) also described adverse effects of cortisone in guinea pigs infected with tuberculosis. Michael, Cummings and Bloom (29) utilizing the rat, which develops a chronic non-fatal granulomatous process after administration of human tubercle bacilli, reported that all of the animals receiving only tubercle bacilli survived, in contrast to 20% survival in those receiving cortisone and tubercle bacilli. In the cortisone treated animals the histologic lesions were more diffuse and contained fewer inflammatory cells. Turner and Hollander (30) administered cortisone daily to rabbits with typical erythematous dermal syphilomas due to *Treponema pallidum*. In 48 hours the lesions became filled with a mucoid material and then enlarged steadily. In 15-25 days the lesions ruptured with extrusion of mucoid material. This material contained much larger numbers of actively motile *T. pallidum* than were found in controls. Withdrawal of the cortisone was followed by reappearance of the erythema and induration and rapid enlargement of the lesion, but spontaneous resolution of the lesions even-

tually occurred as in the controls. Histologically the lesions in the cortisone treated rabbits showed large well demarcated areas of poorly stained material with relative few mononuclear cells. This decrease in inflammatory cells and increase in acellular material was also found in biopsies taken before, during and after cortisone therapy. When cortisone was discontinued, there was a return to the more usual picture. In addition large numbers of dead *Treponema* were found in the cortisone treated animals after receiving penicillin for 24-48 hours while in the controls no spirochetes were found. Schwartzman (31) reported that cortisone in combination with ACTH markedly accelerated poliomyelitis infection in mice and enhanced markedly the susceptibility of hamsters to this infection. ACTH without cortisone failed to produce this effect and Schwartzman attributed this to the elaboration of an unknown factor capable of reversing the enhancing effect of cortisone. Glaser *et al.* (32) felt that ACTH or cortisone treated mice receiving streptococci intranasally did not fare as well as controls, while Mogabgab and Thomas (33) found an increased susceptibility of rabbits to streptococcal infection after four days of pretreatment with cortisone. These animals died in 2-12 days with septicemia and some had abscesses in the heart and kidneys; the control animals survived. In addition mention was made of a glomerular lesion resembling acute glomerulonephritis. Loosli *et al.* (34) found that ACTH had no effect upon influenza A virus infection in ferrets or mice. In our laboratories we have shown (12) that mice, receiving cortisone subcutaneously on two successive days and on the third day 0.1 cc. of a twenty-four hour broth culture of *C. kutscheri* subcutaneously, develop macroscopic abscesses in many of their organs and *Corynebacteria* can be cultured from these foci. Visceral abscesses were found in only two mice out of a total of fifteen controls receiving *C. kutscheri* but no cortisone. In both of these the abscesses were present in the lung only. In the cortisone treated animals, on the other hand, macroscopic abscesses were present in six of the eleven mice. Five of these had liver abscesses, four had kidney abscesses, three had heart abscesses and five had lung abscesses. Solotorovsky, Gregory and Stoerk (35) reported that mice infected with *M. tuberculosis* of reduced virulence showed increased susceptibility to infection after cortisone. They also found that survival of vaccinated mice after infection with a highly virulent strain was decreased in cortisone treated mice. These investigators confirmed the diagnosis of tuberculosis as the cause of death by histological examination and the finding of acid-fast bacilli. Milzer (36) however, found that neither ACTH nor cortisone altered the course of experimental poliomyelitis or equine encephalitis infection. Lurie *et al.* (37) noted a greater development of the tubercle bacillus in the lungs of cortisone treated animals. Kilbourne and Horsfall (38) noted an increased multiplication of viruses in embryonated eggs injected with cortisone. At the 2nd Clinical ACTH Conference the effect of ACTH on two protozoal diseases was described. Gil, Perrin and Balcazar (39) reported survival and clinical improvement in the myocarditis of Chagas' disease in 2 dogs. However, cultures remained positive and organisms were still present in minimal lesions. It is noteworthy that intercurrent bronchopneumonia caused death in one animal. Kass *et al.* (40)

noted the development of blackwater fever in all of 4 monkeys infected with *Plasmodium knowlesi* but a similar progress of the disease to death in both treated and control animals occurred regardless of this complication. An increase in circulating parasite counts was noted in humans with chronic vivax malaria after ACTH. It is tempting to mention the inhibitory effects of cortisone upon the phagocytic cells of the reticuloendothelial system in an attempt to explain these phenomena. A further example of the effect of cortisone on protozoal infections are reported by Wolf, Kabat, Bezer and Fonseca (41) who stated that in the course of experiments in allergic encephalomyelitis, *Macacus rhesus* monkeys of Indian origin were found to be infected with *Trypanosoma cruzi*. Of 20 animals that received no cortisone, none showed trypanosomal lesions although two had trypanosomes in their blood. 22 of 79 animals receiving cortisone developed visceral lesions of trypanosomiasis. 16 additional monkeys had lesions resembling those of trypanosomiasis but were free of parasites. Kligman, Baldridge, Rebell and Pillsbury (42) infected guinea pigs with *Trichophyton mentagrophytes*, vaccinia virus and *Staphylococcus aureus*. Cortisone prolonged the incubation period of the fungus infection. The average time for healing was 55 days with cortisone treatment as compared with 32 days in the controls. In addition, the lesions remained at a maximum for about a month in the former as compared to about 1 week for the latter. In the former trichophyton were present in skin scrapings for about 35 days while they were present for about 25 days in the latter. If cortisone was given at the climax of the infection, the healing time was prolonged for two weeks. With vaccinia virus, the primary infection was more severe in cortisone treated animals and the healing was slower. In the animals intradermally infected with *Staphylococcus aureus*, the lesions were more severe in the cortisone treated animals. Kass *et al.* (43) reported that mice passively protected against a virulent pneumococcus died more rapidly if they also received cortisone. Cortisone treatment also was associated with a higher mortality rate in adult mice infected with influenza virus. Kilbourne and Horsfall (44) have similarly been able to induce lethal infection with Coxsackie virus in adult mice by administering massive doses of cortisone. These animals would ordinarily be resistant to infection with this organism. Weiss and one of the authors (45) found that inoculation of a strain of an unadapted influenza B virus into cortisone treated mice produced significant increase in mortality and an increase in the number of animals with striking histologic changes in the bronchi and parenchyma. Abernathy (46) administered cortisone to mice, guinea pigs and rabbits infected with *Brucella abortus*, *B. mellitensis* and *B. suis*. With cortisone there was an increased death rate and more wide distribution of the lesions. Hepatic granulomata were converted into necrotic lesions. This was most pronounced with *B. suis*. Glaser (47) produced streptococcal and pneumococcal pneumonia in rats by intrabronchial inoculation. A less favorable survival with cortisone and also a relatively less cellular edema fluid with more bacteria were found in the cortisone treated animals. Vollmer and Hurlbut (48) found that massive doses of cortisone increased the mortality of mice infected with Japanese B encephalitis virus while moderate doses of

ACTH or cortisone had no adverse effect upon the disease process. Bloch, Venesland and Gurney (49) found that cortisone promoted the earlier stages of development of tuberculosis in guinea pigs. Hypersensitivity was inhibited in 50% and cortisone interfered with streptomycin therapy of the disease. They stated that much of the early mortality seen in the cortisone treated group was due to "intercurrent non-specific infection, most frequently pneumonia" especially with larger doses of cortisone. The effects of cortisone upon the disease were more pronounced in animals receiving cortisone from the day of infection as contrasted to animals who were first treated with cortisone 24 days after infection. They state "these findings indicate that cortisone promotes the development of tuberculosis in the guinea pig, especially during the early state of infection, and apparently particularly so during the first rise in hypersensitivity."

At the 1st Clinical ACTH Conference cases were reported illustrating a lack of therapeutic effect for this agent in virus pneumonia, pneumococcal pneumonia, poliomyelitis and tuberculosis even though such phenomena as defervescence of fever, increased appetite and a sense of well-being were expressed in almost every case (50).

Further detailed clinical studies of attempts at the therapy of acute infections in humans were described several months later (51, 52). No evidence was obtained of any bactericidal action exerted by adrenal steroids in the pneumonias. Nevertheless the patients remained asymptomatic and afebrile while a rusty sputum persisted in one case and bacteremia in another. A third patient developed an empyema. In line with experimental observations, several preliminary reports of attempts to bring the chronic inflammatory diseases with granulomatous reactions under control through the use of ACTH alone or with antibiotics were reported at the 2nd Clinical ACTH Conference (53). Amelioration of the lepromatous lepra reaction (53a), clearing of the laryngeal lesions of tuberculosis with questionable pulmonary improvement (53b), and no improvement in cutaneous and systemic North American blastomycosis were reported (53c). Finland (54) suggested at this time that the use of ACTH and adrenal hormones be deferred in the treatment of acute infections because of "the possibility that they will mask important symptoms and signs of illness." The course of typhoid fever has been reported to be beneficially influenced by cortisone alone or by cortisone and chloramphenicol in combination (55, 56). Simpson, Rosenblum, Wood and Stammer (57) used cortisone acetate locally in congenital syphilitic interstitial keratitis with good results. In the light of our experimental experience caution is required even in local cortisone therapy. Although very little if any systemic absorption occurs, particularly if no active infection is present locally, or if effective antibiotic therapy is added, this mode of treatment should be employed with careful and frequent observation for a spread of the infection or the superimposition of a new infection. More recently the reported experiences with the spontaneous development of pseudotuberculosis and other infections in cortisone treated mice and rats (3, 12, 21-23) were paralleled by the development of true tuberculosis in humans during the course of ACTH and cortisone therapy (58-60).

Cortisone and ACTH may indirectly produce serious infection in body cavities as for example peritonitis following perforation of peptic ulcers during the course of therapy of other conditions with these drugs (6, 61-63). The spread of the infection is due primarily to the poor inflammatory and connective tissue reaction (24-26, 64-66), which does not permit walling off and sealing of the ulcer, thus increasing the possibility of perforation with resultant peritonitis caused by organisms present in the gastrointestinal tract.

All of the above indicate that the administration of cortisone and ACTH is hazardous in patients with infections, and even in those cases in which no infection is present continuous vigilance must be exercised in order that the spontaneous or subclinical infection which might become evident on clinical examination be promptly and properly treated. This admonition is not only based upon the experimental and clinical data outlined above but also upon the modified inflammatory reaction and healing process following the use of these substances.

DISCUSSION

The administration of cortisone produces anatomic changes which in many respects are similar to those described by Selye (67) after the administration of alarm producing agents, except that in cortisone treated animals there is atrophy of the adrenal cortex and pituitary instead of the hypertrophy which accompanies the alarm reaction. This indicates that cortisone may be a hormone capable of eliciting the alarm reaction without the intermediary of the pituitary or the adrenal cortex. Thus cortisone may prove to be an agent of value not only for the study of the shock mechanism and its relation to infections but also as an added tool for the analysis of the mechanism of infection.

It has been shown that cortisone depresses antibodies (12, 68-71), as does "severe stress" (22, 72-74). The experimental data seem to indicate that at least one and perhaps more factors play a role in the decrease in circulating antibody. If cortisone is administered after the animal has been immunized there is a rapid decrease in circulating antibody as part of the general protein catabolic effect of the hormone; since the catabolic effect during active immunization may proceed at a slower rate than antibody formation, its action could explain the "inhibition" in antibody production described in animals receiving multiple doses of cortisone during the period of immunization. The protein catabolic effect might also deprive the antibody-forming source of its antibody precursors. Germuth and Ottinger (68) attributed the poor antibody response to a suppressing action of cortisone on antibody formation (anti-anabolic effect). However, this effect alone cannot explain the precipitous fall in antibody titer seen in immunized animals within 24-48 hours after cortisone (12, 70) if the life of the antibody molecule is much longer than this short period of time. Refractoriness to reimmunization for as long as 9 weeks after cortisone administration (12, 75) has been observed. Whether this represents a temporary damage to the site of antibody formation, a blocking or inhibition of factors regulating antibody release into the circulation, or other mechanisms cannot as yet be stated. The

desired clinical effects of cortisone however, are due in part to the amelioration of the antigen-antibody reaction since sufficient antibody is no longer available for this reaction. On the other hand since antibodies, which offer a major resistance to unrestricted multiplication of organisms, are now diminished or absent, there is unlimited propagation of the organisms. The absence of the bacteriostatic effect of antibody permits bacteria to multiply in certain tissues and actually form colonies as though they were growing in enriched culture media. As a corollary to this, organisms which under normal circumstances are harmless, become highly pathogenic in subjects receiving cortisone. It is apparent that the same mechanism, i.e., the effect on antibody, which on one hand has a beneficial action through obviating the violent antigen-antibody reaction, may on the other hand produce deleterious results by depressing and exhausting protective mechanisms including antibodies.

Because the antigen-antibody reaction as a rule produces a predominantly inflammatory reaction which masks the degenerative changes, the elimination of the antibody depresses the masking inflammatory element and discloses a purer direct degenerative change in susceptible tissue. In this manner, cortisone can be used to delineate with less difficulty the inflammatory from the direct degenerative effect. Since in the final analysis control of infection may be traced predominantly to antibodies which offer considerable resistance to the growth of bacteria, the absence of this protective mechanism, as was indicated above, permits the bacteria to multiply locally, forming large colonies and, as might be anticipated, if toxins are produced in susceptible tissues, severe degeneration and necrosis with slight or absent inflammatory reaction is seen in areas adjacent to the bacterial colonies. Histologic pictures such as this with pure colonies of organisms surrounded by areas of necrosis are evident in cortisone treated animals (3, 12, 21, 23). Mice harboring well encapsulated *Cysticercus fasciolaris* when treated with cortisone exhibit striking necrosis in the region surrounding the cyst (12).

Another factor to be considered is the reactivity of individual tissues in animals receiving cortisone, and evidence in the literature indicates that cortisone affects this reactivity in divergent ways. In cortisone treated animals the inflammatory reaction is subdued and inconspicuous with poor fibroblastic proliferation and lack of encapsulation. Other structures and tissues may display diminished reactivity. Thus the cells of the glomerular tufts of cortisone treated mice receiving *C. kutscheri* are comparatively normal, while in the untreated animal administration of the organism produces an abundance of cytoplasm with an increase in the number of nuclei, and occasionally even necrosis of the glomerular capillaries (12). The modified reactivity of the host is further substantiated by the fact that animals receiving cortisone are less capable of withstanding exposure to cold and wetting, particularly immature mice (3). Increased sensitivity after cortisone has been reported in the acute glomerulitis of streptococcus infection (33) and the necrosis surrounding encapsulated *Cysticercus fasciolaris* (12). Even more striking is the modification of inflammatory response in granulomatous diseases. Whereas the *local reaction* to subcutaneously

injected *C. kutscheri* in untreated mice is predominantly one of epithelioid and giant cells (hence the original name of pseudotuberculosis), cortisone treated mice respond to this organism with the formation of abscesses containing numerous broken down polymorphonuclear leucocytes (12, 75). Other granulomatous diseases manifest comparable modifications in their inflammatory patterns (21, 28-30, 39, 46).

The possibility of change in virulence of the organism in cortisone treated animals remains to be proven. This is possible since several animal passages of an organism even in a usually resistant host (12, 31, 44, 45) can be achieved after cortisone administration. The shock effect which is similar to cortisone (3) may be responsible, at least in part, for increased virulence of organisms including viruses in times of famine, war or other great stress and in turn can explain epidemics accompanying these events. This effect also manifests itself in experimental procedures where attempts are made to provide the animals with a favorable environment: drenching with water augmented the effects of cortisone in immature mice (3), in rodents subjected to undue experimental handling there is a lability of peripheral blood counts, the presence of an aggressive "fighter" animal in a group of control animals may modify the findings (76). This latter effect was seen in a group of control mice infected with *C. kutscheri* where such an incident was associated with the death of all of the animals, except the "fighter", from visceral dissemination of the organism as seen following cortisone treatment (75).

Knowledge of the foregoing data has introduced a need for additional precautions in experimental investigation and forcefully indicates the necessity for careful pathological and bacteriological studies in all animals receiving cortisone or ACTH. In our laboratory, before a new strain or source of animals employed for an experiment, we determine the presence of reservoirs of infection or subclinical infection by detailed studies after the administration of repeated daily large doses of cortisone. By this means we have found differences in the type and incidence of infection in various strains and sources of our laboratory animals (75). These precautions are necessary, particularly in the study of physiologic substances, since the element of infection may play a role in the modification of the factors under investigation. In researches in which conclusions are based upon length of survival and mortality, the presence of these adventitious factors or intercurrent fulminating infections may modify the results and invalidate the conclusions. In instances in which the "spontaneous" infection is of a low grade nature and not fatal, it might, in an additive manner, modify the direct observations. One experience of this type is worthy of mention. Renal cortical necrosis and hemorrhagic skin lesions similar to those seen by Thomas and Mogabgab (77) or Thomas and Good (78) have been noted sporadically in mice and rats given a variety of bacteria. (75). Coincidentally and possibly causally related, in each of these animals a latent focus of infection, usually *S. enteritidis*, was present. In some cases these quiescent foci had been activated by "preparatory" doses of cortisone. In rabbits receiving polysaccharides (79-81) a greater frequency of renal cortical necrosis was observed in animals which had latent

Coccidial liver abscesses (83). It is possible that cortisone administration weakened the encapsulating fibrous tissue permitting absorption of cyst products.

Consideration must also be given to the direct pharmacodynamic effect of cortisone as well as to the vehicle in which cortisone is suspended. Menkin (82) has shown that the vehicle in which cortisone is suspended increased capillary permeability.

SUMMARY

1) Cortisone depresses antibodies and therefore may suppress a harmful antigen-antibody reaction but at the same time permit multiplication in the body of a dormant pathogenic or ordinarily non-pathogenic organism.

2) Cortisone may serve as a tool in the study of the inflammatory mechanism. It can serve as a means of producing a direct degenerative tissue reaction due to antigen without a complicating antigen-antibody inflammatory factor.

3) Cortisone may alter the reactivity of the host tissue, so that some tissues will resist a degeneration producing stimulus while others will react to produce unusually severe degeneration and necrosis.

4) Cortisone permits growth and multiplication of organisms thus making possible serial passage of organisms in species which are normally resistant to the multiplication of the organisms.

5) Cortisone can be used to determine the presence of reservoirs of infections or subclinical infections in animals. In investigations with cortisone and ACTH in which survival, mortality and morbidity are determining factors, the presence of these reservoirs must be ruled out.

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HUMAN AND EXPERIMENTAL ARTERIOSCLEROSIS*

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INTRODUCTION

The term "arteriosclerosis" is often used rather loosely, if not to say indiscriminately, for a variety of unrelated disease entities. Employing the term in its literal sense, one would have to include any condition which leads to hardening of the arterial wall. In its true meaning, however, arteriosclerosis denotes a limited group of distinct degenerative arterial diseases, possibly interrelated, and characterized by localization and specific pathologic anatomical appearance. In this light it seems justified that the term arteriosclerosis does not encompass the manifold pictures of arteritis related to infection or allergic states such as syphilitic, typhoidal or rheumatic lesions, or inflammatory conditions of the polyarteritis nodosa or thrombangitis obliterans type. And yet it must be admitted that the separation of degenerative from inflammatory lesions cannot be too sharp because the end results of arteritis may be indistinguishable in many instances from those of so-called purely degenerative changes. It should also be remembered that among the etiological factors considered of importance in arteriosclerosis, infection cannot be ruled out as one of the many possible noxious agents.

In clinical arteriosclerosis, five entities may be distinguished:

1) *Simple arteriosclerosis of the elderly*, produced by the "wear and tear" of aging, consisting in loss of vascular elasticity and consequent stretching and tortuosity;

2) *Arteriosclerosis* which is closely allied with hypertension, associated with marked medial hypertrophy and degeneration, as well as proliferative thickening of the subendothelial layer of the intima in precapillary arterioles;

3) *Arteriosclerosis of the Moenckeberg type*, showing primary necrosis and calcification of the media as the characteristic lesion, responsible for the beaded and pipe stem appearance of medium sized arteries of the limbs, considered by some the cause of intermittent claudication of the elderly;

4) *Cystic medial necrosis of the aorta* first described by Erdheim, consisting of focal areas of mucoid degeneration in the aortic media which may lead to vacuolation, recognized today as the cause of dissecting aneurysm of the aorta; and finally,

5) *Atheroma or atherosclerosis* consisting in deposits of cholesterol esters in the

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intimal tissues followed by calcification, apparently due to a combination of injury to the arterial wall and disturbance in the lipid metabolism.

The presence of any of these five disease entities does not exclude the simultaneous presence of any or all of the others. In fact it has remained a moot question whether they are variations of the same disease or whether they have an entirely unrelated etiology.

Atherosclerosis is clinically the most important lesion and therefore has been the subject of intensive clinical and animal experimental investigations. In view of the vast amount of work done in this field, one is inclined to regard with some disappointment the slow advances in our concepts on etiology of atheroma and even more the modest success of our prophylactic and therapeutic efforts against this condition in the 38 years since Anitschkow (1) first induced atherosclerosis in rabbits by feeding pure cholesterol. And yet, today as then, many workers in this field doubt the identity or even close relationship of human atheroma to lesions produced in the experimental animal by cholesterol feeding. It is pointed out rightfully that the feeding of excessive amounts of cholesterol (0.5 to 1 gm daily), causes distinct vascular changes only in rabbits, less clear cut lesions in guinea pigs and either no changes or minor and insignificant lesions in carnivores and omnivores. Furthermore, it is objected that atheroma in man is not generally nor necessarily accompanied by cholesterolemia.

Nevertheless, there are many factors in favor of a correlation with human atherosclerosis. It has been demonstrated by several authors that the majority of patients under 60 years of age who had coronary occlusion show increased blood cholesterol levels. In addition, hypercholesterolemia is known to be present in other conditions frequently associated with the development of atherosclerosis and disturbance of the lipid metabolism, such as hypothyroidism, diabetes mellitus, essential xanthomatosis, and the nephrotic complex in nephrosclerosis.

Recently, moreover, it has been demonstrated that the absence of increased cholesterol blood levels is no proof of a normal cholesterol metabolism. There may exist a disturbance in the equilibrium of cholesterol and phospholipids in the blood affecting the degree and stability of their colloidal dispersion and producing a tendency to the formation of coarse aggregates (cholesterol bearing giant molecules of Gofman and associates (2)). As a result, precipitation of these aggregates may take place within the arterial intima, probably at sites previously damaged by the mechanical pounding of the blood or other noxious agents. Owing to the chemically inert nature of cholesterol, such intimal films may impair the normal exchanges of gases and nutritive substances across the interface between blood and intima and thus give rise to the development of lesions characteristic for atherosclerosis.

While these newer concepts add considerable weight to the argument concerning the important contributory influence of cholesterol in the development of human atherosclerosis, they actually represent only slight modifications of the old theories of Virchow and his school (3). Indeed, the classical introductory remarks of Ludwig Aschoff (4) to the excellent monograph on arteriosclerosis pub-

lished by the Josiah Macy, Jr. Foundation in 1933 could preface any modern book on this subject without change and with few additions.

Perusal of the enormous experimental literature on arteriosclerosis reveals that a seemingly disproportionately large majority of studies consists in variations of the "theme of Anitschkow," the influence of cholesterol feeding. Surprisingly little attention is given to the primary damage of the arterial wall, although its existence is postulated by most authorities today. Moreover, throughout the years there has developed a growing trend toward the biochemical approach in research on arteriosclerosis, and unfortunately a correspondingly increasing neglect of systematic morphological studies. It would seem that closer attention to histological alterations of experimental vascular lesions at various stages of their development might offer some new clues to the pathogenesis of arteriosclerosis in man. In addition much emphasis is being placed upon reproducing the exact picture of human atherosclerosis and upon finding dissimilarities or similarities between spontaneous and experimental arteriosclerotic lesions. It might be more profitable to investigate any change which can be elicited under standardized conditions in the vessel wall of animals, whether or not they should be regarded as arteriosclerotic, *sensu strictiori* (5). Thus, it seems to us, we may uncover an overall similarity in the basic pattern of vascular lesions, irrespective of the mode of production, but conditioned by the specific reaction of a highly specialized tissue to injury.

In the following a brief account will be given of results obtained in experimental studies scattered over a period of almost eight years and previously reported only in preliminary form (6, 7, 8, 9). It should be stressed at the outset that these studies were not concerned with cholesterol arteriosclerosis and that the lesions produced do not resemble atherosclerosis. Rather they are similar to alterations seen in human disease entities which primarily affect the arterial media.

In 1940 in the course of toxicity studies with sulfonamide drugs (10), it was discovered that following excessive dosages of sparingly soluble sulfonamides, albino rats may develop severe sclerosis of the stem and larger branches of the arterial tree, with the aortic arch as the predilection site of the most frequent and most extensive damage (11, 12).

Based on these findings a method for the production of experimental arterial injury was developed (6) with the aim of exploring the pathogenesis of this vascular alteration and of searching for prophylactic and therapeutic measures against arterial lesions. It could be established that both incidence and severity of the vascular damage are substantially increased by the administration of sodium chloride in excess, and diminished in the presence of ammonium chloride. Efforts were then directed towards improvement of the method of production of arterial injury. The goal was twofold: simplification of the procedure and achievement of the highest possible incidence of vascular alterations. After numerous trials over a period of years, a well standardized and extremely simple procedure was evolved which induces almost invariably extensive damage to the arterial tree and other serious organic changes within a matter of a few days (13).

MATERIALS AND METHODS

Closely bred adult albino rats of both sexes from our own colony were used. The animals had been raised and maintained on a standard commercial diet. Excessive dosages of sparingly soluble sulfonamides were injected as aqueous solutions of their sodium salts, usually by the intraperitoneal route, over a long period of time, or at a single occasion, in order to produce a renal block. The exact procedure used in early experiments has been described elsewhere in detail (6). In most of these experiments in which sodium sulfadiazine served as the noxious agent, volume, specific gravity, pH and sulfonamide concentration in the urine were recorded daily and the N.P.N. and sulfonamide level in the blood were determined at frequent intervals.

In the more recent studies, sodium N_4 -acetyl sulfathiazole was selected for the production of renal obstruction. A single intraperitoneal injection of 0.5 gm per kg body weight in male rats or 0.4 gm per kg in female rats, causes without exception long lasting deposition of sparingly soluble acetyl sulfathiazole crystals in the renal tubules. In these newer experiments, in addition to the analytic procedures outlined above, the blood pressure was followed throughout each test by recording the volume change in the hind leg of the unheated, unanesthetized rat with the help of a photoelectric tensometer (14).

The duration of an individual study was from six days in some tests with single injection of the noxious agent, to periods of more than 9 weeks in experiments with chronic sulfonamide injection. At the termination of an experiment, the animals were killed by exsanguination in ether anesthesia and the blood was collected for additional chemical analysis, including in some experiments estimation of calcium and phosphorus levels in the serum. A thorough post mortem examination of all organs was then carried out. As far as feasible, animals succumbing during an experiment also were autopsied.

Special attention was given to the gross appearance of the aorta and its larger branches, the heart, the stomach, the thymus gland, the thyroid, the parathyroids, the adrenals and the kidneys. All important organs of each animal were preserved in 5% formaldehyde or other fixing solutions for histological study. Sections were made of all organs enumerated above and in addition also of lungs, liver, spleen, pancreas and striated muscle. Hematoxylin-eosin stains were made for all tissue sections and supplemented whenever necessary by special stains.

Preliminary studies of a similar type were also done in rabbits.

RESULTS

1. *Production of Arterial Damage*

The results to be described are those obtained with the latest single dose modification of the original procedure, using sodium acetyl sulfathiazole as the noxious agent. Although, on the whole, results were closely similar to those achieved with the older methods of production (6, 7), the present procedure showed greater consistency and uniformity of organic alterations, most of the lesions being of advanced degree. Thus far, a total of 96 male and female rats have been subjected to the procedure outlined with essentially identical results.

a) *Symptoms and signs following renal obstruction.* For the first 24 hours following the injection of the noxious agent the animals manifested oliguria or complete anuria. Thereafter most of the rats developed gross hematuria and increasingly excessive polyuria which remained as a permanent sign of the irreversible renal injury. For several days all animals appeared ill and depressed and ate very little. Death occurred in about 30 per cent of young male animals, usually not before the fifth day of the intoxication; older rats (300 days plus) proved more

resistant with regard to the lethal effect of the intoxication. Female rats rarely succumbed to the smaller dosage selected for them. In fact, the entire clinical course of the intoxication was substantially milder in female animals.

There was a considerable initial loss of body weight which was usually not completely equalized even in animals surviving for weeks. Between the tenth to fifteenth day of the intoxication calcium levels in the serum were found to be within normal range, whereas inorganic phosphate concentrations were elevated to two to three times above the normal values and the non-protein nitrogen levels had risen to between 80 and 260 mg per cent. As a rule the blood pressure rose to hypertensive levels, starting at about the third to fifth day after the renal injury and climbing steadily to average systolic pressure values of 200 mm Hg at about two weeks after the injection. Thereafter, there was a gradual return to normotensive levels, most animals reaching their original normal blood pressure about three to four weeks after the injury. Mean systolic blood pressure levels and daily urine volume of a group of 15 male rats following renal injury by sodium acetyl sulfathiazole are illustrated in Fig. 1. In general the blood pressure curves of individual animals showed no substantial deviation from the indicated mean. In other experiments blood pressure readings of 300 mm Hg and above were recorded at several occasions.

b) *Important pathologic-anatomical alterations.* The nature and incidence of organic changes are exemplified in Table I which illustrates the results achieved with a representative group of 21 male albino rats. It is apparent that alterations usually of an advanced degree were produced almost invariably in all five organs listed. A detailed analysis of the pathologic anatomical changes of these and other organs will be given elsewhere. The present description will concentrate upon a brief summary of the macroscopic and histological appearance of cardiovascular and renal alterations.

The damage in the arterial tree usually affected the aorta in its entire thoracic and abdominal course and extended into many of its large branches (Fig. 2). In most instances the change was conspicuous on gross examination. The damaged vessels were converted into inelastic, thickened, friable tubes. The injury seemed most pronounced at points of mechanical stress, especially at the aortic arch, and as a rule decreased in severity with increasing distance from the heart. In the majority of animals the aortic arch was the site of multiple saccular or diffuse aneurysmic dilatations. Calcium deposition was at times diffuse, producing a "pipe stem" aorta, but more often segmental, resulting in the formation of bulging calcified rings which gave the aorta a "goose's trachea" or "bamboo stick" appearance, a picture well known in human medial sclerosis of Moenckeborg. Occasionally hyalinization, especially of the dilated aortic arch was so advanced that this structure appeared to possess the consistency and transparency of glass.

Under the microscope degeneration and necrosis seemed to be initiated in the smooth muscle fibers of the aortic media which became swollen and basophilic and later disintegrated into structureless granular clumps. This was followed by swelling and disintegration of its elastic membranes and finally imbibition

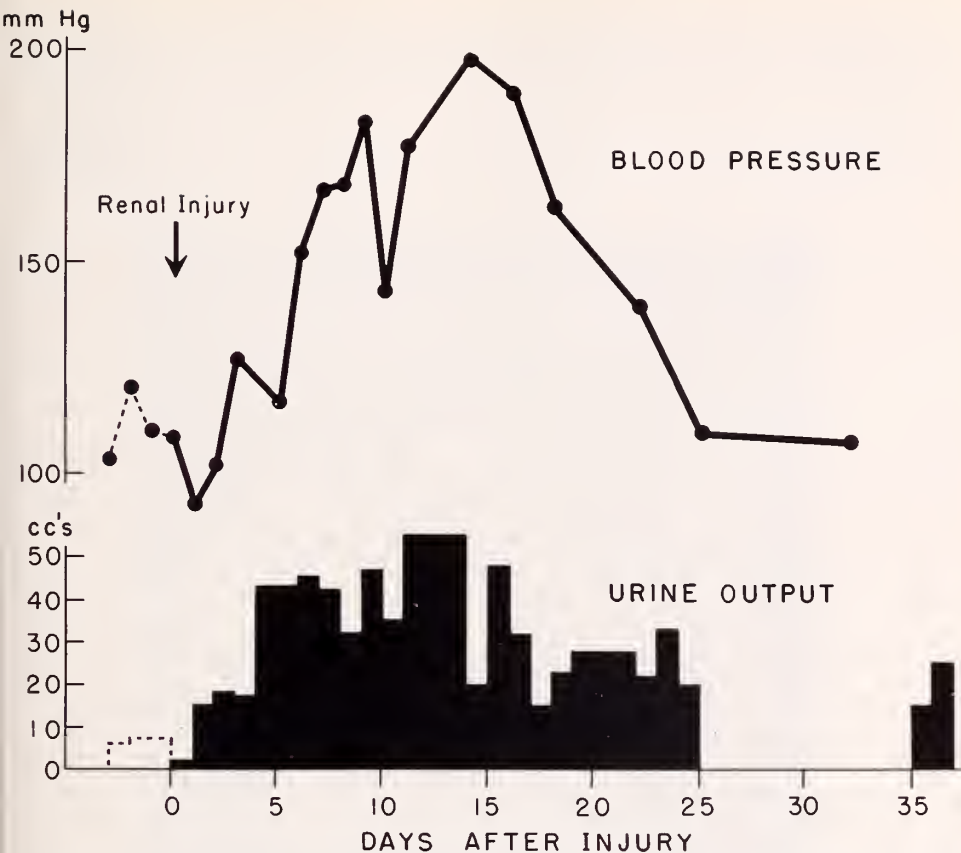


FIG. 1. Mean systolic blood pressure and mean daily urine volume (per animal) of 15 male albino rats before and after renal injury. Each point of the blood pressure curve represents the average of 4 to 6 consecutive readings.

TABLE I

Important pathologic-anatomical alterations in albino rats following a renal block with sodium N^4 -acetyl sulfathiazole

(Single intraperitoneal injection of 0.5 gm/kg body weight in 21 male animals)

ORGAN	TYPE OF LESION	NO. OF ALTERATIONS		TOTAL INCIDENCE PER CENT
		Moderate	Advanced	
Heart	Focal myocardial necrosis or perivascular infiltration of coronary arteries or both	5	12	81
Aorta and large branches	Medionecrosis and calcification	1	20	100
Thymus	Atrophy, fibrosis	—	21	100
Adrenals	Hypertrophy	5	16	100
Kidneys	Calcifying nephrosis	—	21	100
	Pyelo-nephritis			
	Interstitial nephritis			

of the necrotic tissue with calcium salts. The intima was initially not involved, but showed in areas overlying extensive medial injury reactive reparative proliferation.

In the heart the injury consisted in numerous pinhead to rice kernel size foci of muscular necrosis, often visible to the naked eye as distinct greyish white



FIG. 2. Medionecrosis and "bamboo-stick" calcification of the aorta in the albino rat. The heart was turned over in order to bring the aortic arch into full view. Note that the rigid arch was broken in preparation. Also visible are the swollen kidneys and the enlarged right adrenal (the left gland was removed).

elevations of the epicardial surface (Fig. 3). Histological examination revealed that the necrotic muscle fibers were surrounded by leukocytic and large mononuclear infiltrations, followed in older lesions by fibroblastic proliferation and finally scar formation. In addition the coronary arteries exhibited in many instances perivascular infiltrations with large mononuclear cells and occasionally also necrotic areas within the vessel wall.

The cardiovascular alterations were apparently consistently preceded by severe renal damage. The kidneys appeared greatly enlarged and edematous. The moist organ weight was usually about double that of the normal kidney weight. On crosssection the obstruction of renal tubules by sulfonamide crystals was clearly visible to the naked eye in form of yellowish white streaks which diverged in fan



FIG. 3. Necrosis and calcification of the myocardium in the albino rat. Note the patchy white Calcium deposits in the dorsal wall of the left ventricle and the rigid calcified arch of the "bamboo-stick" aorta.

like fashion from the papillary part of the renal medulla towards the cortex. Following a single injection of sodium acetyl sulfathiazole, such crystalline deposits were found within the kidneys for several weeks in gradually diminishing quantities.

The microscope uncovered excessive dilatation of renal tubules with epithelial degeneration and necrosis. Many tubules contained cellular debris, red blood cells and especially pus cells as a sign of ascending infection. The interstitium

showed many areas densely infiltrated with mononuclear cells. This early stage was followed by calcification of necrotic tissue (calcifying nephrosis) and epithelial regeneration, as well as tubular obliteration, cyst formation and proliferative interstitial nephritis.

The pathologic anatomical picture in female rats was identical in all respects with the one in male rats despite the milder course of intoxication.

Using the single dose procedure with sodium acetyl sulfathiazole as the noxious agent, the overall incidence of cardiac and aortic lesions varied between 70 and 100 per cent in individual experiments, whereas not one of the 96 rats escaped serious renal injury. Occasionally myocardial necrosis was found in the absence of

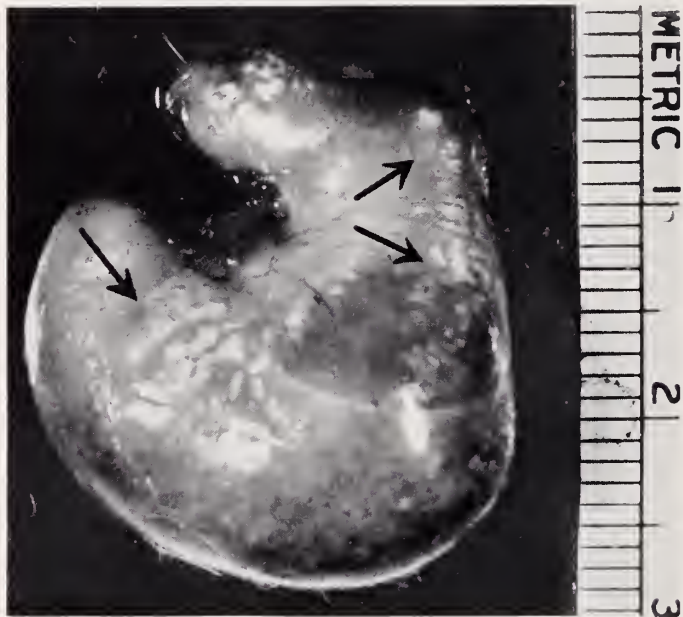


FIG. 4. Necrosis and calcification in the muscularis of the stomach wall in the albino rat. Note the parallel ridges indicated by arrows.

aortic alterations. Older rats of both sexes (300 days plus) appeared to develop substantially more severe injury to the heart, aorta and kidneys, a remarkable fact which requires further exploration.

Table I also indicates that adrenal hypertrophy and thymic atrophy were invariable features of the intoxication. These changes were conspicuous on gross inspection since the weight of the adrenals had increased to about two to four times the normal values whereas that of the thymus gland had decreased by about the same amount. Three rats of the series illustrated in the table showed, in addition, necrosis and calcification in muscle fibers of the stomach wall, visible through the serosa as numerous parallel white ridges which seemed to follow the course of branching gastric vessels on the ventral and dorsal surface of the stomach (Fig. 4). Finally, the parathyroid glands appeared distinctly hypertrophic in most animals. Similar observations were made in other experiments.

It should be stressed that the renal as well as cardiovascular lesions were found to be developed to their fullest extent within five to six days following the renal injury. Rats permitted to survive for longer periods of time (2-5 weeks), showed apparently little further progression of the injury, but correspondingly increasing degrees of reparative changes in the damaged organs, such as scar formation and intense calcification of necrotic areas.

Preliminary results in rabbits indicate that similar cardiovascular alterations can be induced in this species with the help of the present method.

2. *The Significance of Renal Injury in the Development of Arterial Alterations*

It was assumed early in this work that the arterial damage was closely related to the renal injury if not one of its consequences. In order to clarify this causal relationship, an attempt was made either to protect the kidneys from obstruction by the simultaneous administration of sodium bicarbonate (alkalization), or to increase renal injury by overloading with sodium in the presence of an acid urine (sodium chloride), or by marked acidification of the urine (ammonium chloride)

TABLE II

Influence of concomitant alkalization and acidification upon the development of organic changes in aorta and kidneys of albino rats due to chronic intraperitoneal injection of sodium sulfadiazine

FORCING OF FLUIDS BY GAVAGE	RANGE OF URINARY pH	NO. OF RATS	NO. DEAD	DIED WITHIN DAYS	INCIDENCE OF LESIONS	
					<i>Aorta</i> Medio necrosis	<i>Kidney</i> Calcif. nephrosis
Water only (control).....	7.0-7.5	10	4	30-32	6	8
NaHCO ₃ in water.....	7.8-8.6	10	0	—	0	1
NH ₄ Cl in water.....	5.9-6.3	10	8	28-31	1	10
NaCl in water.....	6.5-6.8	10	8	30-33	10	10

(6, 9). Sulfadiazine was used as the noxious agent in these experiments since the solubility of this drug and its acetylated metabolite is most significantly raised by alkalization. The results of a typical representative experiment are summarized in Table II. The table demonstrates that protection of the kidney by alkalization prevented the development of renal obstruction in the animals except one which showed moderate kidney damage, and also obviated the occurrence of arterial injury. All ten rats survived. However, in similar experiments in which a renal block developed because of inadequate alkalization, severe arterial alterations did occur.

If sodium chloride, which has an acidifying effect, was used instead of sodium bicarbonate, most animals showed, as expected, a substantial aggravation of renal injury if compared to the control group. In addition, the sodium chloride treated rats exhibited most consistently the severest degrees of arteriosclerosis with true bony metaplasia in some instances. The use of the stronger acidifier, ammonium chloride, on the other hand, was able to effect complete prevention of the vascular injury although obstructive nephropathy was about as severe as in the sodium chloride treated rats.

Further confirmation of the preventive action of ammonium chloride against arterial injury and the aggravating effect of sodium chloride was obtained in numerous trials employing modifications of the original procedure, such as incorporation of the two salts in the drinking water.

COMMENTS

The evidence presented suggests that medionecrosis and calcification of the stem and larger branches of the arterial tree, produced in albino rats with the help of the present method, is a consequence of renal dysfunction since prevention of injury to the kidney also obviates the pathologic changes in the aorta, whereas aggravation of the renal lesion may result in more severe vascular alterations.

Some of the pathologic anatomical features of this experimental lesion bear a resemblance to the picture of metastatic calcification, which is apparently dependent upon the presence of severe renal impairment, a fact already known to Virchow (15) and later restated by Barr (16) in his well known review on the subject. While Barr held that calcific lesions are located chiefly in the kidneys, heart, gastric mucosa and lungs, it appears from the reported cases of this syndrome that medial sclerosis of peripheral arteries is about as frequently encountered (17). The occurrence of calcium deposits in the soft tissues in renal osteitis fibrosa ("renal rickets") was first mentioned as an integral feature of this syndrome by Albright and his associates (18). Today it would appear that renal insufficiency with secondary hyperparathyroidism is one of the most common causes of metastatic calcification. Herbert et al. (19) consider the alteration of the calcium and phosphate equilibrium in the blood, due to renal disease, as the important physiologic mechanism. With the retention of phosphates in renal insufficiency there is initially a concomitant decrease in the serum calcium level. Stimulation of the parathyroid glands by the increased phosphate or decreased calcium concentration in the blood stream induces mobilization of calcium from the bones. This results in elevation of the calcium level to near normal or slightly above normal levels. The inadequate phosphate excretion may cause oversaturation of the blood with calcium and phosphate ions which promotes the deposition of calcium phosphate into tissues where conditions are favorable. Herbert and associates emphasized that it is necessary for the calcium to be at or near normal values, as well as for the phosphate levels to be elevated, before calcium deposits could occur in the soft tissues.

It seems significant in this connection that in one of our experiments with a group of 14 male rats which were permitted to survive for 10 to 15 days after sustaining the renal injury, phosphate levels in the serum were found to be two to three times as high as in the controls, whereas calcium levels were normal or only slightly below normal. All rats of this particular series showed extensive calcification of the arterial tree and hypertrophy of the parathyroid glands. Thus the secondary calcium imbibition observed in our experimental lesion would seem satisfactorily explained.

However, an answer remains to be found for the more important primary

muscular necrosis in arteries, heart and stomach, since in true metastatic calcification there is believed to exist no evidence that the organs involved have been the site of any previous destructive change. The fact that a single obstructive dose of a bacteriostatically inactive, poorly soluble, conjugated sulfonamide is able to induce the type of alterations reported, would seem to militate against a specific drug action as well as against the allergic nature of the injury. One would feel more inclined to implicate again the severe renal dysfunction as the responsible mechanism.

The importance of the damaged kidney in the development of arterial necrosis has been demonstrated by several investigators. McCormick and Holman (20) reported that acute necrotizing arteritis can be produced with regularity in healthy adult mongrel dogs by feeding a specified high fat diet (containing cod liver oil or creamery butter) for a period of 8 weeks and then sacrificing these dogs through renal injury produced by uranium nitrate, mercuric chloride or bilateral nephrectomy. With this "standard high fat diet" and "standard renal damage" typical arterial lesions could be produced in 36 of 40 animals (90 per cent). Renal damage seemed absolutely essential. Damage to organs and tissues other than the kidneys failed to produce arterial lesions. Hopps and Wissler (21) found that two of six rabbits which received repeated large dosages of sulfadiazine, in addition to horse serum, and developed the typical picture of "obstructive nephropathy," also showed cystic medial necrosis of the aorta. The probable relationship between renal damage and aortic necrosis was apparently not suspected by these authors. Grollman and associates (22) found necrosis of the myocardium and of muscle fibers in the arterial media of dogs subjected to bilateral nephrectomy or to ureteral ligation.

These findings lend support to the viewpoint that a renal factor is responsible for the muscular necrosis observed in the present study in the wall of the arteries, heart and stomach. A causal relationship possibly also exists between the dysfunction of the kidney and the development of adrenal hypertrophy as well as thymic atrophy.

In reporting the opposite effects of sodium chloride and ammonium chloride upon medionecrosis of the aorta in 1943 (6), one of us (D. L.) considered the overloading with sodium as the cause for the aggravation of the aortic injury and the pronounced acidification of tissues as responsible for the prophylactic effect of ammonium chloride. Subsequently Selye and his associates (23) fully concurred with this point of view while demonstrating the protective action of ammonium chloride against periarteritis nodosa-like alterations induced in rats by desoxycorticosterone. Later More and McLean (24) considered the possibility that experimentally induced desoxycorticosterone arteritis and foreign protein arteritis might have a common pathogenesis, mediated through alterations of the serum sodium/chloride ratio as suggested by Selye for desoxycorticosterone. Their results indicated that foreign protein (horse serum) arteritis of rabbits is not mediated through this mechanism. Nevertheless, there was a decreased incidence of arteritis in the group of animals receiving horse serum plus ammonium chloride.

It is conceivable that the prophylactic effectiveness of ammonium chloride against three differently induced arterial lesions might yet provide a clue to some common denominator in the mechanism of their development.

The transient but pronounced elevation of the blood pressure might have been caused by the enormous initial swelling of the obstructed kidneys. In such instances the renal capsule, holding the swollen parenchyma of the kidney like a vise within its rigid confines, could induce hypertension by a mechanism not unlike that operative in cellophane wrapping or Latex encapsulation of the kidneys. In favor of this viewpoint is the fact that the reemergence of normotensive levels seemed to coincide well in time with the disappearance of crystalline precipitate from the renal tubules, the return of the moist kidney weight to within the normal range and the beginning of the healing phase of the renal injury. The invariable finding of adrenal cortical hypertrophy and the probable sodium retention which can be postulated on this basis or on the ground of the severe renal dysfunction might be important contributory factors in the development of hypertension, since desoxycorticosterone (25) as well as sodium chloride (26) are used in standardized methods for the production of hypertension in the rat. Experimental renal hypertension, on the other hand, is known to induce secondary hypertrophy of the cortex and medulla of the adrenal gland (27, 28).

A thorough search of the literature on experimental arteriosclerosis failed to reveal any other method which could induce—without direct mechanical, chemical or thermal interference with the vessel wall—the type, extent and high incidence of grossly visible injury to the arterial tree obtainable with the help of the present procedure.

It is hoped that the simplicity and reliability of this short term method will permit the study of many factors considered of significance in the prevention and therapy of arterial and possibly also myocardial injury. The influence of various dietary, hormonal and mineral metabolic factors is at present under investigation.

SUMMARY

1) Disease entities encompassed by the term human arteriosclerosis are briefly outlined and their relationship to experimental arteriosclerosis is discussed.

2) A simple and reliable short-term procedure for the production of severe medionecrosis and calcification of the arterial tree and of myocardial necrosis in the albino rat is presented.

3) Serious dysfunction of the kidney, induced by this procedure, is believed to be the mechanism responsible for both the muscular necrosis and the secondary calcification in the wall of the aorta, the heart and the stomach. The concomitant pronounced but transient hypertension is explained as being also renal in origin.

4) It is demonstrated that overloading with sodium chloride induces marked accentuation of the arterial injury, whereas ammonium chloride in similar dosage inhibits the development of arterial alterations.

5) The gross and microscopic appearance of the renal and cardio-vascular injury is briefly described.

6) The direction of present studies using this short-term method for the production of cardio-vascular alterations is touched upon.

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ZUR FRAGE DER ÜBERTRAGUNG SENSIBLER IMPULSE IM RÜCKENMARK DES FRÖSCHES*

(ERSTE MITTEILUNG: HISTAMIN)

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Seitdem Loewi (1) mit der vor nunmehr 30 Jahren erfolgten Veröffentlichung "Über die humorale Übertragbarkeit der Herznervenwirkung" seine epochemachenden Arbeiten eingeleitet hatte, in denen die chemische Wirkung der postganglionären Nervenenden des autonomen Systems auf ihre Erfolgsorgane nachgewiesen wurde und mit der Entdeckung der Cholinesterasehemmung durch Physostigmin gleichzeitig dessen Wirkungsmechanismus erklärt werden konnte (2), sind zahlreiche Forscher dem Problem nachgegangen, auch für die sensible Sphäre Überträgersubstanzen, deren abbauende Fermente und hemmende Stoffe für diese aufzufinden und zu identifizieren. Loewi (3) selbst hat darauf hingewiesen, dass die sensiblen Rückenmarkswurzeln acetylcholinfrei seien, woraus gefolgert werden kann, dass hier das Acetylcholin, welches bekanntlich (4) auch an so vielen anderen Nervenschaltstellen, wie an den intermediären autonomen Ganglienzellen und an den Synapsen der motorischen Spinalnervenenden, die Rolle des Überträgerstoffes spielt, dass Dale (5) die inzwischen eingebürgerte Nomenklatur "cholinerg" (und "adrenerg") vorgeschlagen hat, für die Impulsübermittlung nicht in Frage zu kommen scheint, sondern eine andere bezw. andere Substanzen für diese Aufgabe verantwortlich zu machen seien. In diese Richtung wiesen auch die alten, bis dahin unverständlichen Versuche von Langley und Anderson (6), wonach es z. B. nicht gelungen ist, sensible mit cholinergen Fasern durch eine Naht zu funktioneller Vereinigung zu bringen.

In den letzten Jahren haben sich vor allem Umrath und Hellauer (7) (8) mit der Frage der Aktionssubstanz sensibler Nerven beschäftigt und Florey (9) hat "Vorkommen und Funktion sensibler Erregungssubstanzen und sie abbauende Fermente im Tierreich" untersucht sowie auf interessante Beziehungen zur zoologischen Systematik hingewiesen. Die erstgenannten Autoren konnten in Versuchen, die sie mit Extrakten ventraler bezw. dorsaler Rückenmarkswurzeln am entnervten Kaninchenohr durchführten, Unterschiede dieser in der Wirkung auf die über einen Axonreflex gesteuerte Kapillarweite beobachten. Obwohl die Meinungen über die Art des Überträgerstoffes im Axonreflex auseinandergehen, indem Lewis und Marvin (10) das Histamin, Dale und Gaddum (11) hingegen das Acetylcholin als Überträgerstoff in diesem Axonreflex ansprechen, konnte in den Versuchen an dem Ohrtest gezeigt werden, dass die Wirkungen von Acetylcholin, Histamin, Ventral- und Dorsalextrakt der Rückenmarkswurzeln verschiedenartig und gegeneinander abzugrenzen sind. Die Autoren (7) (8) postulieren daher eine eigene "sensible Substanz," welche sie mit ihrer Ausschlussmethode am entnervten Kaninchenohr identifizieren zu

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können glauben. Häusler und Hellauer (12) haben versucht, durch photoelektrische Messung der kapillarerweiternden Wirkung der Aktionssubstanz sensibler Nerven im Ohrtest diese Methode zu objektivieren, wenn sie sich auch bewusst waren, dass damit an dem prinzipiellen Nachteil dieses Testes nichts geändert wird, nämlich an seinem Mangel an Spezifität, da ja bereits viele körpereigene Substanzen als kapillarerweiternd erkannt worden sind. So sind denn auch die Untersuchungen von Umrath und Hellauer (7) (8) mit Hilfe des Axonreflexes nicht unwidersprochen geblieben (13) und es lag deshalb in unserem Bestreben, eine prinzipiell andere Methodik zu finden. Unser Gedankengang war dabei folgender: Bei Reizung einer unteren Extremität eines Frosches müsste in seinem Rückenmark jene "sensible Substanz" frei werden, welche für die Reflexübertragung auf die motorischen Vorderhornganglienzellen verantwortlich ist. Um diese Substanz zu gewinnen, erschien es uns notwendig, in irgendeiner zu eindeutigen Schlüssen berechtigenden Form eine Rückenmarkspfusion vorzunehmen. Wir verwendeten viel Mühe und Zeit, für das Rückenmark die Kibjakow'sche Idee (14) einer Perfusion über das Gefässsystem zu einer brauchbaren Methode zu gestalten, wie das an intermediären autonomen Ganglien mit bekanntem Erfolg gelungen ist (15). Leider war es auf diese Art und Weise weder bei Fröschen noch bei unseren, gegen die langdauernde Präparation widerstandsfähigeren, Kröten möglich, zu leistungsfähigen, Präparaten zu kommen, vor allem auch nicht, die über das Gefässsystem einflussende Perfusionsflüssigkeit wiederum an einer bestimmten Stelle, nämlich durch eine vom Rückenmark kommende Vene, exakt zu sammeln. Wir versuchten daher schliesslich, das Rückenmark in seiner natürlichen Umhüllung zu um- (und durch-)spülen und bedienten uns zu diesem Zweck des Wirbelkanals als eines natürlichen Durchflussraumes, indem wir im Bereich der Halswirbelsäule eine Kanüle in das dort durch die vorangegangene Decerebrierung entstandene Wirbelloch einbanden. Das untere Ende der Wirbelsäule wurde abgeschnitten, wodurch es möglich war, das—gegebenenfalls mit sensibler Substanz angereicherte—Perfusat wiederzugewinnen, welches daraufhin an einem geeigneten Testobjekt zu prüfen war. Als solches bot sich uns der kontralaterale Reflexbogen eines zweiten Frosches dar, der zur Rückenmarkspfusion auf die gleiche Weise präpariert, zusätzlich jedoch gleichzeitig als Reflexfrosch verwendet wurde. Der Reflexbogen läuft in diesem Falle mit seinem afferenten Teil von dem einen Bein, welches elektrisch oder mechanisch gereizt wird, zum Rückenmark, wird dort umgeschaltet und geht efferent zum anderen, dem registrierenden Reflexbein. Gibt es nun eine bei sensibler Reizung im Rückenmark freiwerdende Substanz, die in das Perfusat übergeht, so müsste bezw. könnte sie, dem zweiten, dem Testfrosch perfundiert, bei diesem reflexartige Kontraktionen hervorrufen und des weiteren durch exakte Austestung ihre Natur zu identifizieren erlauben. Überdies müsste die Rückenmarkspfusion solcher Präparate pharmakologische Beeinflussungen des Reflexbogens bezw. seiner zentralen Teile und damit zusammenhängende Fragestellungen zu untersuchen erlauben.

METHODIK

I. Präparation des ersten Frosches zur Gewinnung der "sensiblen Substanz": Ein Frosch (*R. esculenta*) wird auf die übliche Weise decerebriert und zwar wird die dazu dienende Metallspitze von einem Punkt, der in der Mitte der Verbindungslinie zwischen den beiden *Ossa quadrata* liegt, gegen das Gehirn vorgetrieben. Im Anschluss daran wird von cranial her in dieses Bohrloch eine Kanüle in den Wirbelkanal eingebunden. Der Frosch wird dann evisceriert, die Haut über dem Abdomen, dem halben Rücken und den unteren Extremitäten abgezogen und nach beiderseitiger Freilegung der Nn. ischiadici bis zu ihrem Austritt aus dem Rückenmark die Wirbelsäule knapp darunter abgeschnitten, so dass nach Durchtrennung der Bauchhaut seitlich der Wirbelsäule das Präparat schliesslich nur mehr aus Kopf, Thorax, oberen Extremitäten, dreiviertel der Wirbelsäule und dem aus ihr austretenden Plexus mit den Nn. ischiadici besteht. Schliesslich wurden an den mit Ringerlösung feuchtgehaltenen N. ischiadicus der einen Seite in 5 mm. Abstand zwei Elektroden angelegt. Dieses Präparat ist mittels eines durch den Unterkieferbogen geführten Hakens aufgehängt und wird aus einer bis zu 20 cm überhöhten Mariotte'schen Flasche rückenmarkperfundiert. Die von uns verwendete "Frosch-Ringerlösung" hatte folgende Zusammensetzung: NaCl 0,6%, CaCl₂ 0,01%, KCl 0,01%, NaHCO₃ 0,1%, Glukose 0,2%; ohne Glukose "ermüdeten" die Präparate rascher, wie die abfallenden Kontraktionshöhen zeigten. Die Ringerlösung fliesst durch den Wirbelkanal und tropft sowohl aus dem aufgeschnittenen caudalen Wirbelsäulenende als auch aus den Intervertebrallöchern. Es wird lediglich jenes Perfusat aufgefangen, welches aus dem unteren Wirbelsäulenende, also knapp nach der Umspülung des Rückenmarks austropft; die Perfusion erfolgt möglichst langsam, so dass pro Minute nur 1-2 Tropfen ausfliessen. Die vorgelegten Schälchen werden alle 15 min. gewechselt, wodurch Portionen von je ca. 1-2 ml. erhalten werden, und zwar die erste unmittelbar nach der Präparation, welche ja als solche zugleich einen extrem starken sensiblen Reiz darstellt, dann folgen drei Ruheperioden zu je einer Viertelstunde ohne Setzung eines Reizes und schliesslich eine fünfte Periode während einer längeren elektrischen Reizung über die Nn. ischiadici. Mit diesen Portionen wird nun die Rückenmarkspfusion des Testfrosches vorgenommen.

II. Präparation des zweiten Frosches als Testobjekt: Ebenso wie bei dem ersten Präparat wird nach Decerebrierung der Wirbelkanal kanüliert und an eine eigene Mariotte'sche Flasche angeschlossen; es wird ebenfalls das untere Wirbelsäulenende von der darüberliegenden Haut freipräpariert und abgeschnitten, so dass auch hier das Rückenmark in seiner natürlichen Hülle umspült wird und die Perfusions-flüssigkeit frei aus dem unteren Wirbelsäulenende abrinnen kann. Nun wird nach Evisceration die Freilegung der Aorta communis von der Ventralseite her angeschlossen und eine Perfusion der unteren Extremitäten nach der bekannten Methode von Lwen-Trendelenburg (16) angeschlossen. Dies geschieht, erstens um eine Ermüdung der unteren Extremitäten hinauszuschieben und zweitens um die Rückenmarkspfusion sicher von der Durchsplung der Beine zu trennen und auf alle Flle zu verhuten, dass durch abfhrende Gefsse aus dem Rückenmark etwa Perfusat des Wirbelkanals in den brigen Kreislauf gelangen knnte. Auch dieser Frosch wird nach vollendeter Präparation am Mandibularbogen aufgehngt und der dazu verwendete Haken an einem Stativ befestigt; an dieses wird das linke Bein mit einem Faden angebunden und an Knchel und Wade mit je einer Elektrode versehen. Das rechte Bein wird mit einem Schreibhebel verbunden und seine kontralateral ausgelsten oder sonstwie erfolgenden Zuckungen an einem Kymographion registriert. Die Reizung des linken Beines erfolgte durch einen, aus 50-60 mA starken Einzelimpulsen von mglichst kurzer Dauer und Distanz bestehenden, rechtwinkelig zerhackten Gleichstrom, also mit sogenannten faradischen Gleichstromstssen; die Dauer eines solchen Stromstosses betrug eine sec., das Intervall zwischen den Stromstssen 30 sec. Nach je 5 solcher Reize wird eine Pause von 10 min. zur Erholung von Ermdungserscheinungen eingeschaltet.

ERGEBNISSE

A

Zunächst wurden zur Überprüfung dieser neuen Methode an dem Testfrosch, der auf die eben beschriebene II. Art präpariert war, der Rückenmarksp Perfusionsflüssigkeit verschiedene Pharmaka zugesetzt. So beobachteten wir, worüber an anderer Stelle ausführlich berichtet wird (17), dass es unter der Wirkung von *Strychnin*, das der Perfusionsringerlösung zugesetzt war, bei gleichzeitiger elektrischer Reizung, zu einer enormen kontralateralen Reflexsteigerung und Kon-

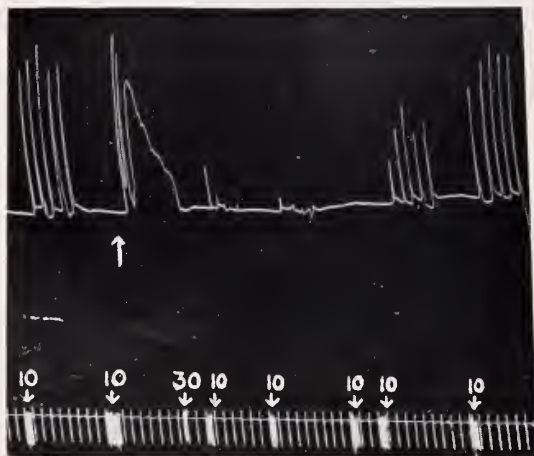


ABB. 1



ABB. 2

ABB. 1. Kontraktionen des Beines auf kontralaterale elektrische Reizung bzw. auf Histamin: ↑ 0,01 mg. Histamin. ↓ Kymographionstillstand in min. Zeitschreibung 30 sec.

ABB. 2. Kontraktionen des Beines auf kontralaterale elektrische Reizung bzw. auf Histamin: ↑ 0,001 mg. Histamin. Zeitschreibung 30 sec.

traktionshäufung kam, und *Picrotoxin* hatte einen ähnlichen, wenn auch nicht so ausgesprochenen Effekt, während beispielsweise unter *Pervitin* nur eine leichte Reflexsteigerung zustande kam. Deutlich war diese hingegen unter *Acetylcholin*, dessen Wirkung nach Physostigminzusatz zur Perfusionsflüssigkeit in vielfach verstärktem Masse auftrat, während *Adrenalin* und *Noradrenalin* keinerlei Einfluss auf die elektrisch ausgelöste Reflexfähigkeit hatten.

Waren diese Befunde, besonder etwa beim *Strychnin*, nicht überraschend, so zeigte sich bei der Injektion von *Histamin* (die Angaben in den Legenden zu den Abbildungen beziehen sich auf freie Base, verwendet wurde Histamin-dichlorhydrat in der entsprechend höheren Konzentration) in die Perfusionsflüs-

sigkeit ein ganz neues, unerwartetes Wirkungsbild: Der blosse Zusatz von Histamin rief auch *ohne* vorherige Reizung des linken Beines Spontanzuckungen des rechten, des Reflexbeines hervor (Abb. 1 und 2), während die im vorigen Absatz genannten Substanzen lediglich die durch die elektrischen Reize aus-



ABB. 3



ABB. 4

ABB. 3. Spontankontraktion auf 1 ml. Perfusat der 1. Viertelstunde ↑. Zeitschreibung 30 sec.

ABB. 4. Spontankontraktion auf 2 ml Perfusat der 1. Viertelstunde ↑. Zeitschreibung 30 sec.

gelöste Reflexfähigkeit entweder steigerten oder die Reflexe überhaupt nicht beeinflussten, wie das z. B. bei der adrenergen Gruppe der Fall war. Diese durch Histamin ausgelösten Spontanzuckungen dauerten so lange als durch das Rückenmark Histamin floss, welches wie Abb. 1 und 2 zeigen, des weiteren phänologisch zu einer Kontraktur bezw. Tonuserhöhung der Beinmuskulatur führte,

über deren Charakter Untersuchungen laufen. Dabei war bei der höheren Histamin-dosis von $0,01 \mu\text{g}$ die kontralateral-elektrisch ausgelöste Reflexerregbarkeit nahezu aufgehoben und kehrte erst nach längerer Zeit (30–60 min.) wiederum zur früheren Höhe zurück, wie Abb. 1 deutlich zeigt, wo die Histaminwirkung und deren Abflauen durch die (am Schluss der Methodik erwähnten) je 5 in 30 sec. Abstand erfolgenden Stromstöße "eingerahmt" ist. Demgegenüber zeigt Histamin in geringerer Konzentration (Abb. 2: $0,001 \mu\text{g}$) unmittelbar nach



ABB. 5

ABB. 5. Spontankontraktion auf 1 ml Perfusat der 5. Viertelstunde \uparrow bei gleichzeitiger elektrischer Reizung. Zeitschreibung 30 sec.

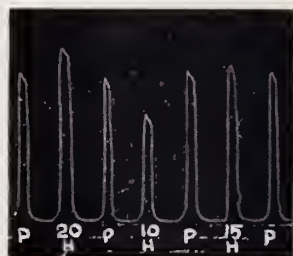


ABB. 6

ABB. 6. Vergleich des Perfusates der 1. Viertelstunde mit Histamin: P = 0,1 ml. Perfusat, H = Histamin in Millimikrogramm.

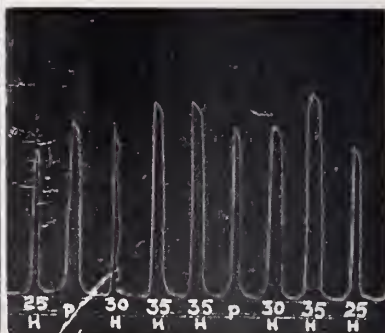


ABB. 7

ABB. 7. Vergleich des Perfusates der 5. Viertelstunde mit Histamin: P = 0,1 ml. Perfusat, H = Histamin in Millimikrogramm.

den auch hier auftretenden Spontanzuckungen eine Amplitudensteigerung der kontralateralen Reflexe.

B

Des weiteren seien nunmehr die ursprünglich beabsichtigten Grundversuche, nämlich die Testung des Perfusates eines gereizten Frosches (Präparat I) am Rückenmark des zweiten (Präparat II) beschrieben. Es wurden der Reihe nach die in der Methodik erwähnten, in kleinen Schälchen aufgefangenen Perfusate aus dem Rückenmark des I. Frosches am II. geprüft. Dabei zeigte sich folgendes: Die Periode (1 ml) aus der 1. Viertelstunde, also knapp nach der Präparation

des I. Frosches, zeigte beim Umfließen des Rückenmarks des II. Frosches (Abb. 3) den gleichen Reaktionstyp, wie er auf Histamininjektion aufgetreten war, sowohl was die Spontanzuckungen und die nachfolgende Kontraktur anlangt, als auch hinsichtlich der wiederkehrenden normalen kontralateralen Reflexe, ja die doppelte Menge, nämlich 2 ml eines solchen Perfusates (Abb. 4) führte zu dem Symptomenkomplex der höheren Histamindosis der Abb. 1. Demgegenüber zeigten sich die Perioden der 2., 3. und 4. Viertelstunde, also die Perfusionsportionen aus Zeitabschnitten, während welcher dem Präparat I kein wie immer gearteter Reiz appliziert worden war, am Testreflexfrosch, dem Präparat II, wirkungslos, d. h. die jeweiligen Stromstöße führten stets zu gleicher Kontraktionshöhe, weshalb es sich auch im Rahmen dieser Arbeit erübrigt, die

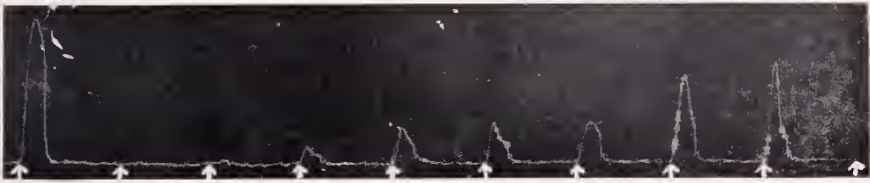


ABB. 8. Hemmung der Wirkung des Perfusats d.1. Viertelstunde durch Dibendrin: \uparrow 0,1 ml. Perfusat d. 1. Viertelst. \downarrow 0,01 mg. Dibendrin.

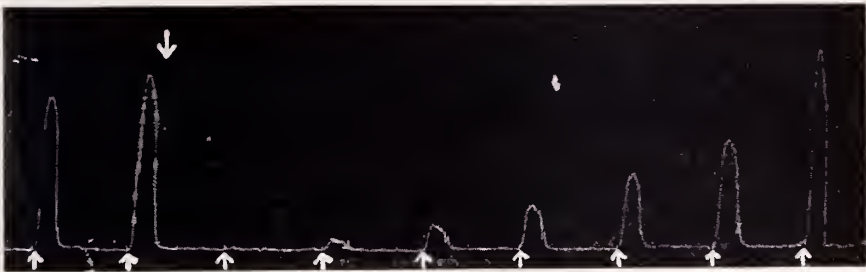


ABB. 9. Hemmung der Wirkung des Perfusates der 5. Viertelstunde durch Dibendrin: \uparrow 0,1 ml. Perfusat der 5. Viertelstunde \downarrow 0,03 mg. Dibendrin.

betreffenden Kurven zu reproduzieren. Dagegen sei in Abb. 5 die Reaktion des Testreflexfrosches II auf Injektion von 1 ml Perfusat gezeigt, das durch das Präparat I geflossen war, während dieses—nach einer Stunde ruhigen Hängens—über seine beiden Nn. ischiadici anhaltend gereizt wurde: Diese Periode aus der 5. Viertelstunde wies wiederum ein ähnliches Wirkungsbild wie die Periode aus der 1. Viertelstunde auf.

Quantitative Auswertungen sind begreiflicherweise mit der in der beschriebenen Form vorliegenden Methodik am Reflexfrosch II nicht möglich, wenn man auch sagen kann, dass das Wirkungsbild von 2 ml Perfusat der 1. Viertelstunde (Abb. 4) etwa 1 ml des Perfusats der 5. Viertelstunde (Abb. 5) entspricht. Es lag nun nahe, die Perfusate in der bekannten Art am Meerschweinchen-Ileum gegenüber Histamin auszuwerten: Die Perioden der 2., 3. und 4. Viertelstunde zeigten auch am Meerschweinchen-Ileum keinen Effekt, dagegen waren die

durch die Perioden der 1. und 5. Viertelstunde ausgelösten Darmkontraktionen histaminartig, d. h. durch Atropin unbeeinflussbar, aber durch Antihistamine hemmbar. Die quantitative komparative Testung gegenüber Histamin ergab für 0,1 ml der Periode der 1. Viertelstunde einen Vergleichswert von 0,015 μg Histamin (Abb. 6), während 0,1 ml der Periode der 5. Viertelstunde einer Menge von 0,03 μg Histamin gleichwertig war (Abb. 7); die erstere wurde durch 0,01 μg Dibendrin gehemmt (Abb. 8), die letztere durch 0,03 μg Dibendrin (Abb. 9).

Die geschilderten Beobachtungen sprechen dafür, dass im Rückenmark des Frosches bei Reizung sensibler Nerven eine Substanz frei wird, die an einem zweiten Froschrückenmarkspräparat einen sensiblen Reiz nachzuahmen imstande ist und sowohl nach der Ähnlichkeit der motorischen Wirkungen als auch nach dem Ergebnis der Auswertung am Meerschweinchen-Ileum als wirkungsgleich (wenn nicht gar identisch mit) dem Histamin bezeichnet werden kann, zumal da Kontraktionen, die durch eventuell freigewordenes Acetylcholin bzw. Kaliumchlorid hätten auftreten können, durch die vergleichende Testung gegenüber Dibendrin ausgeschaltet wurden.

DISKUSSION

Die vorliegenden Ergebnisse beweisen einen Einfluss des Histamins auf Neurone des Rückenmarks; sie zeigen aber auch, dass bei elektrischer Reizung der sensiblen Nerven im Rückenmark eine Substanz auftritt, die nach der vorgenommenen biologischen Prüfung als Histamin bzw. als histaminartig angesprochen werden kann. Diese Befunde stehen im Einklang mit den Untersuchungen von Ungar (18) und von Kwiatkowski (19), welche die Hinterwurzeln, also die sensiblen Teile des Rückenmarks als "histaminerg" bezeichnen; letzterer konnte eine Freisetzung von Histamin bei Reizung der dorsalen Wurzeln von L_V - L_{VII} zeigen, was durch unsere Befunde bekräftigt wird. Diese sind auch mit jüngst bekanntgewordenen Untersuchungen Nordquists (20) zu vereinbaren, wonach die Procainblockade eines Nerven durch Histamin beseitigt werden kann. Bülbring und Burn (21) haben allerdings aus ihren Katzenversuchen am Patellarsehnenreflex, bekanntlich einem Reflex ohne Schaltneurone, geschlossen, dass wegen der entsprechenden Beeinflussbarkeit des Reflexes durch Prostigmin die Ganglienzellen im Rückenmark als "cholinerg" zu bezeichnen wären; dazu sei bemerkt, dass Feldberg und Vogt (22) durch ihre Untersuchungen über den Acetylcholingehalt des Zentralnervensystems beim Hunde zur Feststellung kommen, dass in den motorischen und sensiblen Bahnen des Zentralnervensystems sowohl cholinerge als auch nicht cholinerge Neuronenketten vorhanden sind.

Es erscheint uns jedoch verfrüht, schon jetzt endgültig zu diesen und ähnlichen überaus wertvollen Befunden, sowie zu der eingangs erwähnten umfassenden Darstellung von Florey bzw. bahnbrechenden Arbeitsrichtung von Hellauer und Umrath Stellung zu nehmen, umso mehr als wir gerade mit Versuchen beschäftigt sind, welche die Ergebnisse der letztgenannten Autoren mit unserer Methodik untersuchen, die ja, wie erwähnt, gerade diesem Zwecke dienen sollte.

ZUSAMMENFASSUNG

Es wird eine Perfusionsmethode am Frosch beschrieben, mittels welcher einerseits ein Rückenmarkspcrfusat über die hinteren Wurzeln gereizter Frösche gewonnen wird (Präparat I), andererseits der Einfluss von Pharmaka auf das Rückenmark des Frosches untersucht werden kann (Präparat II).

Aus den Reaktionen des Rückenmarkpräparates II auf *Histamin* sowie aus der Prüfung und Auswertung von mit Hilfe des Präparates I gewonnenen Rückenmarkspcrfusaten kann gefolgert werden, dass bei Reizung sensibler Nerven im Rückenmark des Frosches Histamin bzw. histaminartige Stoffe frei werden, über deren ursächliche bzw. bedingungs-mässige Rolle bei der Übertragung sensibler Impulse weitere Versuche entscheiden müssen.

SUMMARY

A perfusion method of the spinal cord of the frog is described which allows collection of substances liberated during periods of stimulation. These substances are capable of acting like a sensory stimulus on the spinal cord of another animal. When tested on the isolated ileum of the guinea-pig they produce a contraction similar to the one produced by histamine (resistant to atropine and inhibited by antihistaminics). The evidence for and against histamine as transmitter of sensory impulses is discussed.

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INDICATIONS OF BED REST, PARTICULARLY IN THE AGED

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A vigorous trend in general Medicine advocates revision and restriction of the habitual indications of bed rest. I quote only a few of the numerous publications in this line (1, 2, 3). Moreover: "Keep him out of bed!" meaning the aged patient, is a time-honored geriatric advice. This paper expresses opposition to these tendencies to a considerable degree. It is written from the point of view of the internist and geriatrician.

The extreme position is high-lighted by a quotation from William Dock (4): "Absolute bed rest kills more patients than anesthesia and all the drugs of the pharmacopoeia added together."

It would seem to be an apparent contradiction that I do not disagree with the endeavours of surgeons and obstetricians to shorten bed rest after operations and childbirth which are statistically well founded. The approach to these problems is different because an operation in itself is an artificial trauma and childbirth is a physiological process. Neither is a disease. The complications thereafter have in all probability not the same mechanism as in internal ailments.

I do not deny that the new movement contains some sound elements of reform under special conditions, but its exaggeration contradicts clinical experience and common sense, while its uncritical application must endanger many lives.

Bed rest is: 1) a form of partial or complete inactivation by which the patient's exertions are restricted. 2) a relatively horizontal body position; an absolutely flat, log-like immobilization is a rare exception. Changes of posture in bed are easily possible and generally appreciated. An effortless and instant elevation of the thorax for the patient's greater comfort is readily managed in every hospital bed, or in the home with the help of a bed rest or pillow.

Confinement in bed is irksome and may cause some discomfort, depression, difficulties of urination and bowel evacuation. These minor evils are always overcome in every case of essential immobilization.

Certainly, bed rest should never be ordered without due reason and beyond need. Being ambulatory is preferable if feasible. It prevents also loss of calcium and muscle volume. This is partly due to inactivity, but even more to the basic diseases which enforce restricted mobility, such as infections, cancer, arthritis, nervous and muscular afflictions. Active and passive exercise of the muscles can be more easily performed in bed than in a chair, whenever medical indications favor such a procedure.

The most impressive and important arguments presented against bed rest refer to the dangers of venous thrombosis of the lower legs with a consequent

pulmonary embolism and hypostatic pneumonia. The role of bed rest, as such, in their causation can be doubted, even refuted.

In every institution for chronic diseases and for the aged a great number of immobilized victims, young and old, of advanced arthritis, of systemic nervous or muscular affections, of cerebral accidents, are often quite helpless for years. They do not develop venous thrombosis or hypostasis during their prolonged inactivity if an additional disease is not present. Infections, circulatory failure, cachectic illness and operative procedures change the quality of the blood, slow the circulation and favor the incidence of thrombosis.

Since the frequency of venous thrombosis within the leg muscles has been discovered, the influence of a mechanical factor has been stressed: the pressure which a supine position produces on the muscles of the calves. A compression of the veins against the non-elastic interosseous membrane by the weight of the leg and the resistance of the mattress against the muscles may facilitate thrombosis. This is quite possible, if other agents are aiding, but improbable as the sole cause, or chronic immobilization without formation of the thrombi could not be understood.

Even in infections, the tendency to venous thrombosis is not universal. Nothing is more convincing in this respect than the statistics of 750 autopsies from a large tuberculosis hospital (5) where every patient was submitted for months to the strictest type of bed rest without bathroom privilege, and the more advanced cases confined continuously. Signs of pulmonary embolism were only found in 11 of the necropsies. Nine cases were quite hopeless from the beginning and the additional 2 cases had a very doubtful, although not quite desperate, prognosis.

Formation of thrombi is often a sign of impending death and its frequency in autopsies does not allow conclusions to be drawn on the occurrence in the surviving patients having the same alterations.

The most important means of preventing thrombosis are active and passive movements of feet and legs, and careful watching for the first slight clinical signs. There are potent means at hand for treatment, including drugs, nerve block and surgical procedures.

I am in full agreement with recent recommendations of ambulatory treatment in some cases of thrombo-phlebitis. Persons with bland phlebitis, mostly a complication of varicosities, who are otherwise robust, must not be compelled to remain in bed. A permanent elastic bandage (Una boot) decreases the danger of embolism and shortens the duration of the affliction which was formerly treated by complete immobilization for weeks. Lumbar nerve block and the modern anti-coagulants also serve the same purpose.

Operations and childbirth further the formation of thrombi in a manner not quite understood. I am in sympathy with the widespread tendency to permit patients to leave the bed early after operations. The advantages are obvious in the treatment of hip fractures or in pelvic surgery. In operations on the abdomen and chest, the general state of the patient, the presence of malignant or inflammatory disease, the type and extent of the operative intervention have to be carefully taken into consideration, but the principle can be upheld.

The mechanism of thromboses after operations has been painstakingly studied

by the Swiss surgeon K. Lenggenhager (5, 6). Every fresh wound releases substances identical with, or similar to, thrombokinase. They are partially resorbed and, with the prothrombin, calcium and fibrogen of the blood, form ultramicroscopic particles of fibrin which are absorbed on the surface of the platelets, make them viscous and lead to their agglutination. These agglomerates form a sediment where the circulation slows down, *i.e.*, in the large veins of the legs and pelvis and form the head of the thrombus. Fibrin, absorbed, can not be stained in the usual way, but its presence can be demonstrated otherwise, and in new experiments Lenggenhager has clinched his theory. He could imitate the process with citrated blood on a model in glass tubes. The formation of thrombi after wounds depends on the resorption of the noxious substances, the degree of thrombin destruction in the liver and the state of circulation. It can be forestalled by heparin or dicoumarin.

If this is true, then the beginning of postoperative thrombosis is a widely dispersed microscopical coagulation in the circulating blood, whereas the coagulation in disease is massive and localized. It is therefore understandable that the treatment can be different, and that acceleration of circulation by early ambulation can be useful.

In cases where ambulatory treatment is out of question the wider use of the chair, the commode or the bathroom has been advocated, mainly by Dock. This advice doubtless has psychic and material advantages. It is comfortable and a welcome change to sit in a chair, and easier to move one's bowels on a commode. One should make use of these appliances if feasible; but should not forget the exertions made by the patient when he is brought to chair or commode, not forgetting that the increased hydrostatic pressure impairs the circulation in the legs and makes active exercise of their muscles more difficult. The frequent transportations to the chair or toilet give ample opportunity for loosening emboli.

Dock emphasizes the danger of increased venous pressure, for example, during the Valsalva experiment for the loosening of thrombi. It would seem that his preference for the commode is not easily compatible with this warning. What is the advantage of a sitting position for defecation other than a greater ease for the contraction of the abdominal and pelvic muscles? The process of pressing is accompanied by an arrest of the diaphragm and of respiration quite analogous to the Valsalva manoeuvre. It is not infrequent that sudden death occurs in the bathroom, or that during bowel movements severe attacks of coronary failure or cardiac asthma have their commencement. I cannot remember a single case where similar accidents occurred during the passing of stool in bed. One cannot exert the full pressing power in a more horizontal position. Hence the patient's difficulties, but also the avoidance of danger. The physician has to be sure the stools are voluminous and soft, or to recommend an enema.

It has been demonstrated on normal persons and others with compensated heart disease that the oxygen consumption is greater when these persons repeatedly exert Valsalva pressure sitting on a bedpan than if they perform this on a commode (7). This should prove that the commode is less straining for defecation.

Yet, when the indications for a bedpan are really serious, then it is used in

supine position because these patients are either not able to sit in an incommodious position or are forbidden to do so. In the supine position the Valsalva experiment is very insufficient to raise the abdominal pressure—and this is perhaps the greatest advantage of the bedpan. It is also quite a different matter if a compensated heart case walks two steps or if a severely and dangerously ill patient is brought to the commode. The commode is certainly preferable to sitting on a bedpan, if the condition of the patient allows this.

The paramount medical problems are those connected with the extension of bed rest in acute infectious and circulatory disturbances. During acute illness every animal creeps into a quiet, sheltered place and lies down, often omitting the intake of food and water. These instincts speak for themselves. One need only observe the reactions to bodily exertion in seriously ill patients to obtain an answer. No more than supported sitting in a case of pneumonia or severe heart insufficiency accelerates both pulse and respiration. A thorough physical examination or a demonstration to students leaves such a patient exhausted, perspiring and with a tense expression of fatigue. Not without reason did the old physicians enforce the rule that a patient with pneumonia should only be examined once a day and as quickly as possible.

The preference of the hospital residents for a perfect x-ray picture taken in the laboratory instead of using the less brilliant bedside apparatus has caused many complications and relapses, sometimes death. How can it be assumed in serious illness that the way to the bathroom, the transport to the chair or commode is advantageous?

Another point has not been mentioned. Even in an afebrile but severe simple cold we feel every difference of temperature; a slight draught is annoying, although quite negligible in health. The exposed parts of the body, neck and wrist feel cold and often hurt. An unclosed button is a source of discomfort.

All these symptoms are reflected, elicited from the affected organs to the skin. One can influence a gall-bladder colic or ureteral colic by a procaine infiltration of the hyperesthetic zone. It is very probable that these reflexes also work in the opposite direction and that a protection of the skin is advantageous, especially in respiratory infections. Certainly, such a protection can be established in a chair with shawls and rugs. But there always remains the period of transport and installation. Bed is the ideal place for a constant and comfortable temperature of the body surroundings, and all the problems of circulatory adjustment are solved.

The value of bed rest in infections was deeply impressed upon me by observation during the disastrous influenza of 1918 and 1919. Young people had high fever, it dropped and they felt better. They left their bed for bathroom and chair. A day later they relapsed and fatal pneumonia appeared. Since this time I have kept every case of influenza or tonsillitis strictly in bed for the febrile period and an additional few days. I never had reason to regret these precautions, but some patients have paid a high price for their disobedience.

In many acute infections bed rest was the most important therapeutic measure

before the appearance of sulfa drugs and penicillin, preventing complications and shortening diseases. This does not apply to all infectious complaints; urinary infections or malaria allow some license in the young. But complete bed rest is paramount in all the respiratory and most of the acute abdominal conditions, appendicitis, cholecystitis and so on.

In chronic circulatory affections bed rest or chair are a question of the individual case. No general rule applies. As much mobility should be left to the patients as safety permits. The amount varies from being permanently bedridden to systematic gymnastic exercises and taking walks.

Levine (3) reports cases which, ordered to bed with signs of heart failure, develop temporary symptoms of pulmonary congestion, hydrothorax or attacks of dyspnea, at the same time losing their peripheral edema. He suggests overwork of the right heart as an explanation. I would like to stress the mobilization of fluids by bed rest which bring an excess supply of blood to the lung (9). Such an inflow has two different aspects: 1) it is the necessary precondition for the following diuresis and compensation. 2) it may bring the described troubles which are temporary, as Levine asserts also. All the clinical and laboratory signs (decreased serum protein concentration), the effectiveness of morphine and diuretics in cardiac dyspnea and pulmonary edema are in accordance with this assumption.

The acute and chronic forms of orthopnea, caused by various circulatory and respiratory disorders and attacks, are eased by placing the patient in a chair. Its arms give support to the upper extremities and allow muscle groups around the shoulders to become auxiliaries in the respiratory distress.

It is otherwise in acute afflictions such as endocarditis, pericarditis and, most important of all, acute coronary thrombosis. Bed rest is imperative. Complete immobilization and flat posture are exaggerations and not common sense. Movements of the feet should be ordered from the first day, those of the arms are permitted. The position in bed has to suit the patient's comfort.

The prognosis of myocardial infarction has become more favorable during the last decades. This is due to the detection of the clinical and electrocardiographic signs of infarction, permitting an earlier and more precise diagnosis and to the fact that the recognition was followed by the routine of bed rest for 4-6 weeks. Whether the shorter or longer duration is to be decided upon is determined by the severity of the attack, the observation of the electrocardiographic changes, and of the sedimentation rate. The solid basis of this routine is the fact that some weeks are necessary for the resorption of the necrotic parts of the heart muscle, for the formation of a firm scar tissue and the establishment of collateral circulation. The arguments in favor of restricting bed rest essentially to ten days or so are flimsy. Some animal experiments by Harrison are quite irrelevant for the problem and inconclusive in themselves. Prevention of venous thrombosis in the legs has been stressed. We have other means at hand, already mentioned, to do this. Embolization in coronary thrombosis results mainly from intracardial, not peripheral thrombosis. Exertion loosens these thrombi, and one has to wait weeks before organization makes them harmless.

There may be no very great difference in immediate mortality between the two methods. I have no statistical material at hand, but the prolonged period of rest often decides the subsequent course of the disease, the degree of compensation, the frequency of angina pectoris and the recurrence of coronary failure.

The fate of our profession gives warning. Physicians are the worst patients and are the worst treated, because their colleagues make too many concessions to them. The obituaries in the *Journal of American Medical Association* show that a greater percentage dies of coronary thrombosis than in any other group. The reason is that, as a rule, they do not stay in bed for a proper length of time.

A prolonged, intensive study of disease in old age (8) convinced me that the aged should be kept in bed, with the same indications, even more than the young. I was educated in the "keep him out of bed" policy for old people, and I know that the pioneers of Geriatrics in America, Nasher and Thewlis, advocated this routine. Almost every text book recommends it, only Reimann pleads, like myself, for strict bed rest in old age pneumonia.

My change of attitude began when I had the opportunity to direct the treatment of a large group of aged people in a hospital. Pneumonias occurred frequently. I tried to keep them out of bed. The mortality was high. Then I considered the above mentioned observations that stay-in-bed as such did not hurt the aged, and ordered strict bed rest for a control group. These fared better and the routine was changed with the result that the mortality rate sank considerably. Can one really expect the reserve powers of the aged organism to be so much greater than in young persons that the benefits of the bed become unwarranted?

Of the two arguments, venous thrombosis with embolism and hypostasis, the first has been dealt with. It is caused by the disease, not the bed. Hypostasis and terminal pneumonia are frequent complications in senescence; but they are usually signs of circulatory failure, cachectic conditions or decline of vitality. The distinction between primary and secondary pneumonias, between those of secondary and terminal nature is often neglected or not made at all. These differentiations are, however, the clue to the problem.

Primary pneumonias and those following respiratory infections have a decidedly better prognosis with bed rest. I cannot maintain this with equal certainty for the secondary type, subsequent to heart insufficiency or cachexia. But there is no evidence that they can be prevented by the chair or enforced ambulatory treatment. *Hypostasis and terminal pneumonias are nothing but signs of circulatory failure and impending death*; they can be influenced by heart therapy in some instances.

Some benefit of the chair can be conceded in orthopneic conditions, where the depth of respiration may be favored. Otherwise its use only changes the localization of pneumonia and hypostasis from the posterior parts of the lungs to the bases along the diaphragm.

It goes without saying that in the treatment of pneumonia in old age, all the usual methods and available facilities have to be used, and that good nursing care is of the greatest importance, including frequent change of position.

Bed rest is also of the greatest advantage in the acute affections of the upper and lower respiratory tract. None of the complications are encouraged by this regime, especially noticeable is that development of pneumonia is decreased in frequency.

The prevention of chronicity in all acute conditions, as in cystitis, so important in senescence, is also best served by this measure. A severe acute cystitis, enteritis or bronchitis can easily prove fatal in a senile patient within a few days; the intoxication manifests itself mainly in rapid circulatory failure, reacting disastrously to every exertion.

Whenever a senile patient in an acute illness or an exacerbation of a chronic disease becomes febrile, or weak and fatigued, whenever he appears paler or more cyanotic than usual, when his blood pressure drops or his pulse becomes more frequent or small, when his white blood count or sedimentation rate increases—he ought to be in bed. And this, combined with adequate treatment will better his chance for speedy recovery.

In general, the advantages of prudent bed rest in disease prevail over its disadvantages. There is at present no adequate reason for a general reduction of its usual indications, some exceptions admitted. Many more lives are saved by the bed than endangered by it; many more complications prevented than caused, both in the young and in the old.

The medical indications for bed rest suggest new research and need for statistical evidence. Reforms and innovations easily find adherents. The expressed opinions are only conservative for the younger age groups, they are the reverse for senescence. But they may help to reinstate some equilibrium for further investigations.

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EXPERIMENTAL STUDIES ON RENAL CIRCULATION

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In the course of our studies dealing with the pharmacodynamics of the hydro-genated ergot alkaloids, we also investigated the influence of these agents on different types of renal ischemia. A brief preliminary report was presented earlier (1). It can be demonstrated that these ergot derivatives protect the kidneys against various vasoconstrictor procedures such as injection of adrenalin or noradrenalin, general asphyxia or electric stimulation of the nerves surrounding the renal artery (fig. 1).

For the purpose of visualizing the vascular pattern of the kidneys, we used intra-arterial injections of india ink in this series of experiments. The macro- and microscopical study of some 130 kidneys treated in this manner raised many problems of intrarenal blood distribution. We were unable to find in all the expected instances the picture of the bypass mechanism described by Trueta et al. (2). Instead, however, we observed in many experiments an evenly distributed general ischemia of the entire organ, while in others ischemia was observed to be zonally arranged in the cortex and medulla. Furthermore, we obtained preparations which, in the absence of any glomerular filling, demonstrated a well injected capillary network.

In the course of modifying the injection technique, doubts arose in our minds as to the conclusions which can be drawn from such preparations in general. For this reason we decided to supplement our morphological findings with some functional studies, thus assembling more evidence a) for the existence of true arteriovenous channels and b) for a possible diversion of renal cortical blood through medullary bypasses.

METHODS

This series of experiments was carried out on rabbits anesthetized with Nem-butal or urethane. Blood pressure was recorded from a carotid artery. Changes in renal blood flow and in oxygen saturation were registered continuously by a Rein Thermoströmuhr and a photoelectric oxymeter placed on the left renal vein. Kidney volume records were made by connecting an oucometer to a strain-gauge. The trachea was cannulated to record respiration and to allow tracheal occlusion for the induction of general asphyxia. A branch of the external jugular vein was prepared for intravenous injections. The abdominal aorta was ligated below the renal arteries. The coeliac and superior mesenteric arteries were ligated to prevent injection of such vascular areas as the intestines, spleen, or liver. A metal cannula was placed in the abdominal aorta below the origin of the renal vessels and directed upward towards the orifice of the left renal artery. Glass spheres (10–100 microns in diameter), suspended in saline solutions (10 to 20 mg. of spheres/cc.) were injected selectively into the left renal artery.

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RESULTS

I. Arteriovenous anastomoses in the kidney

The anastomotic communications between the arterial and venous beds of the kidney have been the subject of a great number of investigations (3, 4, 5, 6, 7, 8).

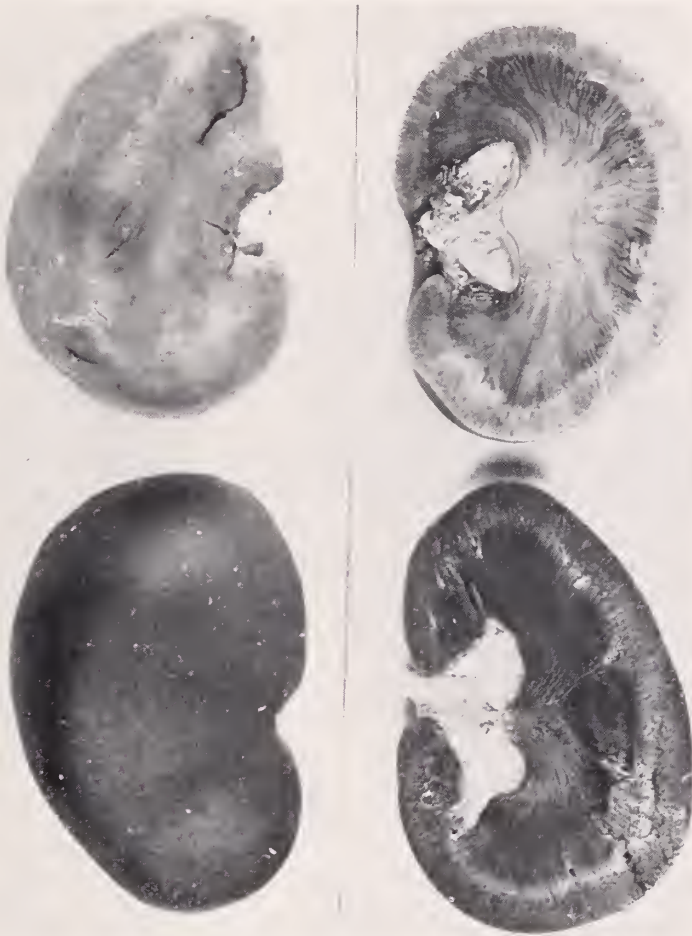


FIG. 1. Aspect of rabbit kidneys injected with india ink during the action of adrenalin. *a.* In the example presented in the upper half of the figure, 10 μ gr. of adrenalin produced a marked ischemia. *b.* After an i.v. injection of hydrogenated ergot alkaloids (0.1 mg/kg of Hydergine which contains equal amounts of Dihydroergocornine, -ristine, and kryptine) no vasoconstriction was manifested during the injection of 20 μ gr. of adrenalin, as shown by the complete irrigation of the kidney with india ink.

It is difficult to determine definitely from the literature whether or not such channels really exist as a functionally significant element of the renal vascular system. Recently, Simkin et al. (9) apparently verified the existence of rather large arteriovenous anastomoses in the renal parenchyma of rabbits. These

authors injected glass spheres into the renal artery of 14 rabbits and were able to recover regularly from the lungs of these rabbits beads not retained in the kidney. It was shown that in most cases spheres of more than $100\ \mu$ diameter had passed both the intact and the decapsulated kidney. We, however, employing Simkin's technic were not able to recover glass spheres in the lungs of our rabbits. The reason for the difference between Simkin's results and ours could perhaps be attributed to the fact that in our experiments the backflow in the inferior caval vein was very much reduced, due to the ligation of the various abdominal vessels. Thus, the relatively heavy glass spheres, after passing through the kidney, would be deposited elsewhere en route to the right heart. This interpretation seems to be supported by the fact, that in two of our experiments beads were found in the inferior vena cava and not in the lungs. On the other hand, one must consider that glass spheres injected into the renal artery without simultaneous prevention of blood flow in the lower abdominal aorta may reach other vascular areas, particularly in the legs, where a-v channels are known to exist.

The histologic study of kidneys injected with glass spheres shows that the beads are localized in the renal cortex exclusively. With small doses, only the peripheral sections of the intralobular arteries are blocked; with increasing doses of glass beads, the deeper cortical zones are also rendered ischemic. Whereas spheres in varying quantity are found in the cortex, not a single one could be detected in the medullary sections of 30 kidneys explored histologically. This would seem to favor the view that the normal medullary blood flow is purely postglomerular.

From a theoretical standpoint, it could be expected that after blocking parts of the capillary circulation with glass spheres, the O_2 -saturation in the venous outflow of the kidney would be maintained or even increased through the a-v channels that might exist. An increase, however, could not be observed in the 8 experiments thus controlled. On the other hand, it was regularly noted that more than one injection of glass spheres was required before any decrease in the venous O_2 -saturation could be recorded, as is shown in the example of fig. 2. Furthermore, the blood flow decreased in only one case after the first injection of glass beads, whereas in six other experiments a second and third injection were required to produce a fall of the flow-curve. In comparing the behavior of blood flow and of venous O_2 -saturation after glass sphere injections, the flow showed a greater tendency to decrease than the O_2 -values (fig. 3). After the blood flow had been reduced by several injections of spheres, there was in most cases a later tendency for it to return towards normal levels (fig. 4 A and B). This might be due to a compensatory hyperemia of those parts of the kidney not yet blocked by the spheres. Such an assumption, however, cannot be accepted without difficulty, if it is remembered that this kind of compensatory regulation develops in the kidney only after hours and days. On the other hand, a participation of a-v anastomoses in this reaction of blood flow could also explain the results.

To sum up, no definite evidence of the existence of functionally important a-v anastomoses was observed in this portion of our study. Assumption of the existence of such channels, however, would facilitate greatly the understanding of

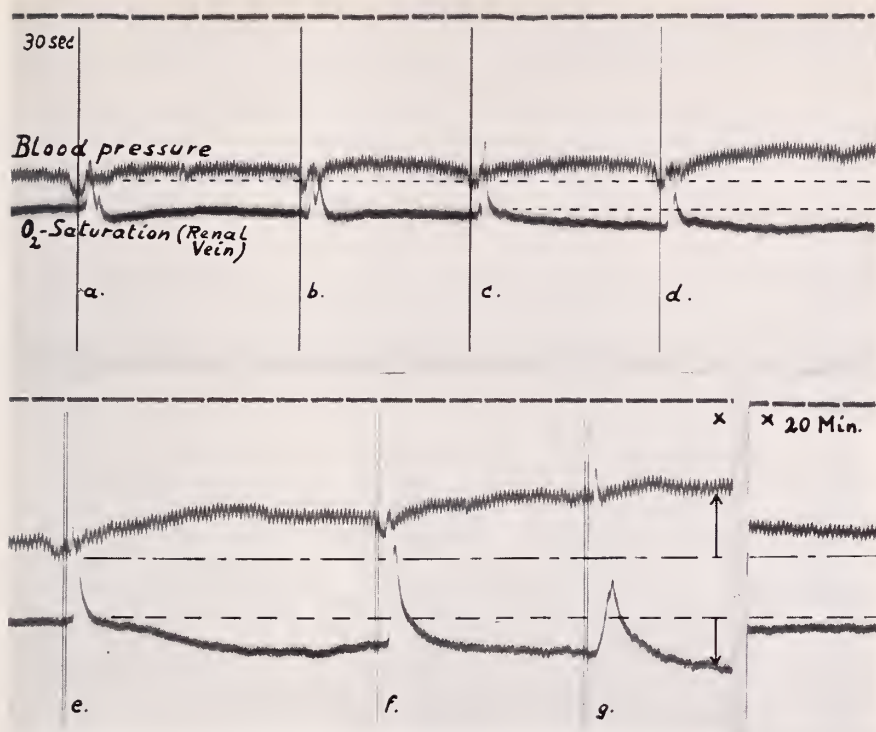


FIG. 2. Effect of repeated injections of glass spheres on the oxygen saturation of the renal vein and on the carotid blood pressure of the rabbit. At each of the points a-g 1 cc. of a suspension of glass spheres in saline (10 mg/cc.) is injected in the renal artery. Whereas the first two injections are without effect, a slight decrease of the O_2 -curve can be seen at c. After an interval of 1 hour after point d, further injections at e, f and g produce an additional decrease in venous O_2 -saturation and a marked increase of blood pressure. Both these changes are transitory, as shown 20 minutes later by the tendency of the pressure- and O_2 -curve to return towards pre-injection levels.

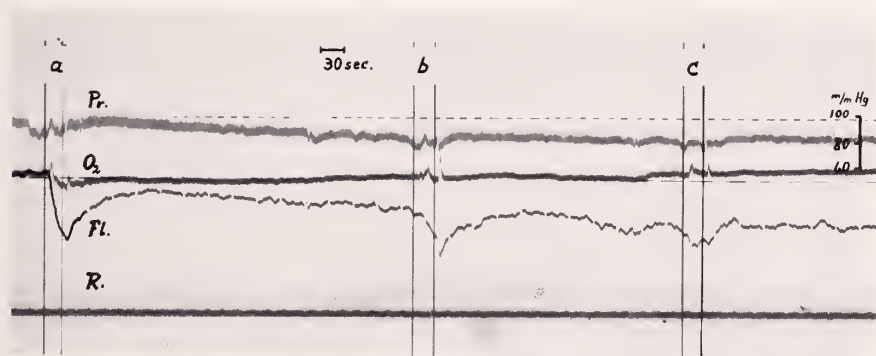


FIG. 3. Simultaneous recording of carotid blood pressure (Pr), O_2 -saturation in the renal vein (O_2), renal blood flow (Fl), and respiration (R) in a rabbit. Effect of repeated injections of 1 cc. glass sphere suspension in saline. The first injection, not shown in this picture, was without any effect, whereas after the second and the following injections (a, b, c) a reduction in blood flow occurs. In spite of this, the venous O_2 -saturation remains essentially unchanged.

renal blood flow and venous oxygen saturation behavior under the influence of repeated glass sphere injections.

II. The Trueta-bypass mechanism

A new basic concept concerning intrarenal blood distribution was advanced by Trueta et al. (2) when they proposed the existence of a possible medullary bypass for the cortical blood flow. Under certain vasoconstrictive influences

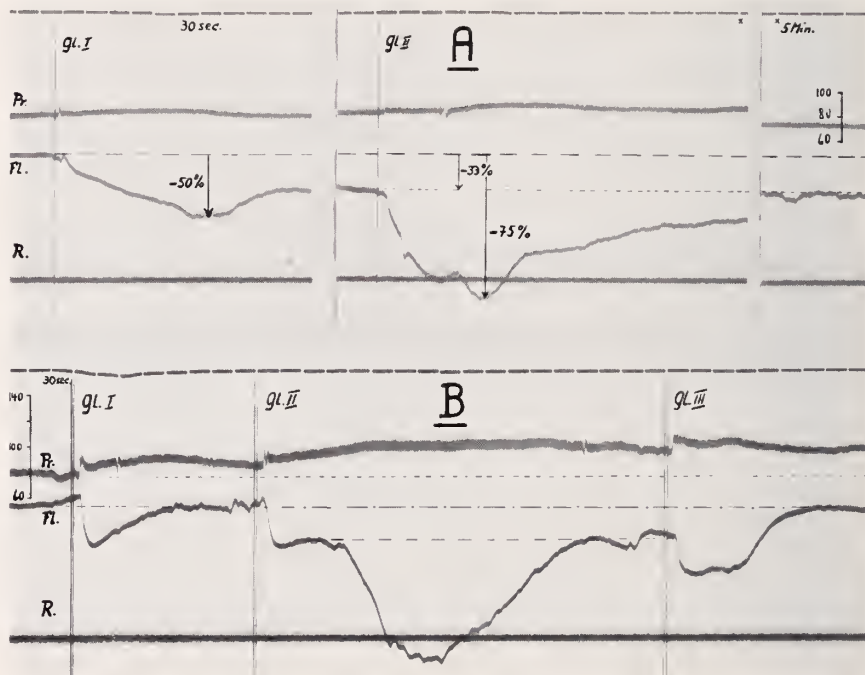


FIG. 4. Record of carotid pressure (Pr), blood flow in the renal vein (Fl), and respiration (R) in two rabbits. A. By an injection of glass spheres into the renal artery at point Gl. I the renal blood flow is first reduced by 50% within 3 minutes, and is then stabilized at a level 33% below the normal. A further injection (Gl. II) results again in a decrease of blood flow to a point 75% below the normal level. The flow starts, however, to improve and is again increased within 10 minutes to the same level as before the second injection. B. This animal shows the same tendency of renal blood flow to recover after having been temporarily reduced by the intra-arterial injections of glass spheres (Gl. I-III). Notice that a few minutes after the third injection the flow is of the same order as before any glass injection.

affecting essentially the cortical vessels of the kidney, the system of juxtamedullary glomeruli would divert part of the normal irrigation of the cortical area to the medulla. In our earlier experiments with intrarenal india ink injections, we had obtained, after adrenalin injection and general asphyxia, some typical pictures of kidney cross sections showing the Trueta phenomenon. These pictures demonstrated an ischemic cortex together with a well filled medullary system. This observation, however, was not a constant one. We endeavored, therefore, to get more information concerning a possible medullary short circuit, by meas-

uring renal blood flow, venous O_2 -saturation and kidney volume following adrenalin injections and under conditions of general asphyxia. Our results were as follows:

a. If Trueta's bypass mechanism exists, it could be predicted that practically no decrease but rather an increase of the O_2 -saturation in the renal vein would result following adrenalin injections. This, however, was not the case. Any dose of adrenalin affecting the venous outflow from the kidney also reduced the renal venous oxygen saturation (fig. 5). Even threshold doses of adrenalin which reduced blood flow slightly and briefly were followed by a temporary fall in the venous O_2 -content. These observations and results are in agreement with those recently published by Moyer, Conn, Markley and Schmidt (10). The observations made during our experiments, in which kidney volume and blood flow were re-corded simultaneously, also suggest that there is no diversion of renal

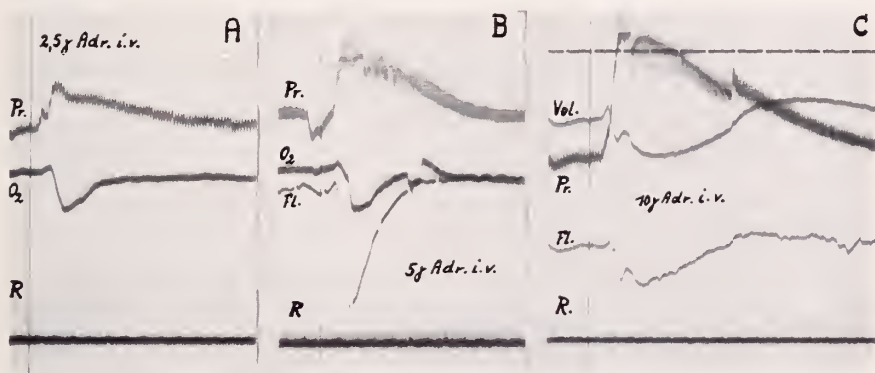


FIG. 5. Examples of adrenalin effects on O_2 -saturation in the renal vein, on blood flow and volume of the kidney. A. Reaction of carotid blood pressure (Pr.) and oxygen content of renal venous blood (O_2) to an i.v. injection of 2.5 μ gr. adrenalin. B. Effect of 5 μ gr. adrenalin on blood pressure (Pr.), O_2 -saturation in the renal vein (O_2), kidney blood flow (Fl), and respiration (R). C. Comparison of the changes of kidney volume (Vol), and renal blood flow (Fl) produced by an i.v. injection of 10 μ gr. adrenalin.

blood flow from the cortex into the medulla during adrenalin vasoconstriction. Both the oncometric and the flow-meter curves are modified in such an identical manner by an adrenalin injection that the existence of a mechanism perceptibly diverting the blood from the cortex to the medulla during adrenalin ischemia must be excluded (fig. 5c).

Another interesting observation was the development of increased sensitivity to adrenalin following injection of the glass spheres (fig. 6). This increased sensitivity was best demonstrated by the behavior of the renal blood flow. It was also manifested by an enhanced and prolonged blood pressure reaction. At present, we do not know whether or not 1) this effect is merely the result of mechanically obliterating parts of the renal vascular bed or 2) whether the development of ischemic zones of the renal cortex through humoral influence leads to an increased adrenalin sensitivity (in the sense of Shorr and Zweifach's VEM effect). The fact that this sensitization to adrenalin becomes apparent only after a

certain time and not soon after the glass sphere injections, would indicate the presence of a mechanism other than a purely mechanical one. Further experiments are needed to clarify this problem.

b. According to Trueta et al. (2) general asphyxia is one of the simplest experimental means of eliciting the renal bypass mechanism. During our earlier investigations with the injection technic (1), we often observed the blanching of the kidney surface while the trachea was clamped for one minute. We were there-

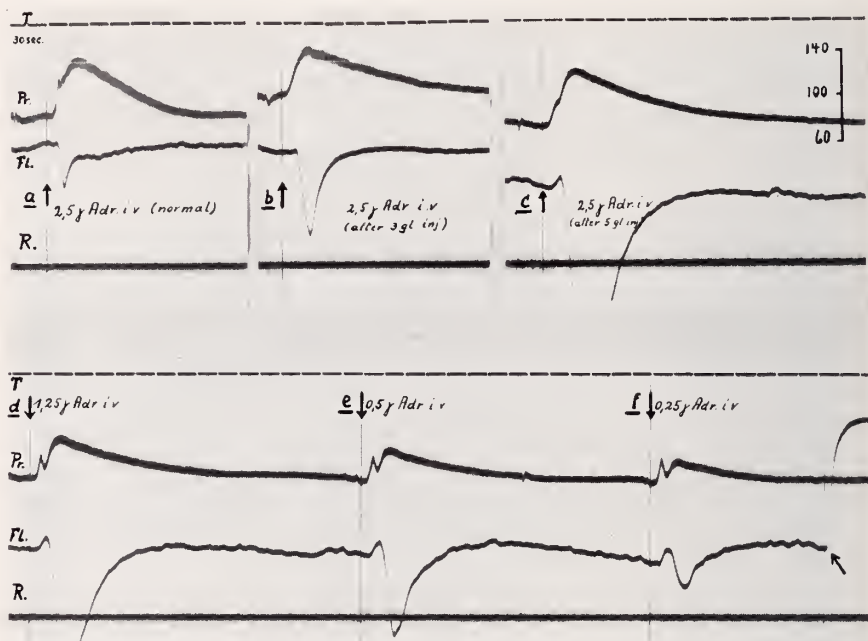


FIG. 6. Example of adrenalin sensitization in the rabbit after partial occlusion of kidney vessels by repeated injections of glass spheres. (Recording of 30 sec.-time intervals (T), carotid blood pressure (Pr), blood flow in the renal vein (Fl), and respiration (R).) At a, the normal response to an i.v. injection of 2.5 μ gr. adrenalin is shown. Between a and b, 3 injections of 1 cc. glass sphere suspension were performed. The same dose of 2.5 μ gr. adrenalin has now a similar effect as produced normally by the double amount of adrenalin. A fourth and a fifth injection of glass spheres (between b and c) enhanced the adrenalin response still more. The examples d-f are the uninterrupted continuation of c, and show the increased adrenalin sensitivity of the animal as evidenced by the decreasing doses necessary to produce vasoconstriction. At the end of the experiment the high frequency current of the Thermoströmuhr is turned off (arrow).

fore surprised in the present series of experiments that the renal blood flow was never found to decrease under this same condition. Cortical vasoconstriction together with unaltered total outflow from the organ would surely be good evidence of a renal medullary bypass. Further experiments with oncometric controls, however, proved that also the kidney volume, like the renal blood flow, did not decrease during asphyxia. This observation excluded not only the assumed bypass, but the existence of any renal vasoconstriction.

The discrepancy between these findings and our earlier observations of renal

ischemia during asphyxiation could at first not be explained. The solution was found as soon as the ligatures on the different abdominal vessels (coeliac and mesenteric vessels) were avoided. In this case we observed regularly renal vasoconstriction resulting from systemic asphyxia (fig. 7). Under normal conditions, renal vasoconstriction during severe asphyxia does occur. This type of ischemia too, however, does not seem to be accompanied by any appreciable medullary diversion of cortical blood. The curves reflecting changes of blood flow and of kidney volume parallel each other closely in all cases. It should be expected that slight degrees of vasoconstriction in the outer parts of the kidney would not affect total renal flow but only the kidney volume when a part of the normal cortical blood flow is diverted through the juxtamedullary bypass. With a more developed cortical ischemia and the well-known shrinking of kidney surface, the decrease in organ-volume would be much more pronounced than the decrease in total flow. Such observations, however, could not be made.

The appearance of asphyxial vasoconstriction in the kidney can be completely prevented by artificial narrowing of the total vascular bed with consecutive relative increase in blood volume (fig. 7). Adrenalin liberation from the adrenal gland does not play any role in the development of asphyxial vasoconstriction. The effects of adrenalin are not diminished but always markedly enhanced by this procedure in contrast to the effects of asphyxia. Moreover, the asphyxial vasoconstriction is also abolished by denervation of the kidney (fig. 11).

One must assume that the kidney is only one member in a delicate regulatory system brought into play under asphyxia in order to offer a greater blood supply to the brain and heart. By the preliminary exclusion of important parts of the vascular bed, a relative increase of total blood volume is present. This seems to render a further participation of the kidney in compensatory regulations unnecessary. This view is further supported by the fact that by bleeding such animals we could produce reappearance of the asphyxial renal vasoconstriction.

c. The sphere injection experiments led to a further conclusion concerning Trueta's medullary bypass mechanism. As mentioned above, the injected glass spheres are always found in the intralobular arteries. They appear first in the outer cortex and following repeated injections also in the deeper cortical zones. If india ink is injected at this point, a vascular pattern can be found which resembles very much that of Trueta's phenomenon—the medullary vessels are well filled but no ink is in the cortex. Such a kidney is a good model for the study of medullary flow. As Trueta et al. (2) pointed out, the renal circulation time (the time the blood requires to pass from the renal artery through the kidney and out into the renal vein) would be shorter were the blood to bypass the cortex. The continuous record of O_2 -saturation in the renal venous blood affords the opportunity of measuring the lungs-to-kidney circulation time. Normally, the O_2 -curve begins to increase 10 to 12 seconds after the first postasphyxial respiration (fig. 8). This time indicates the velocity of the blood that flows from the lungs into the renal vein through the left heart, aorta, renal artery and kidney. After injection of the quantities of glass spheres necessary to block most of the outer cortical vascular bed, a decrease in flow velocity was shown in five rabbits

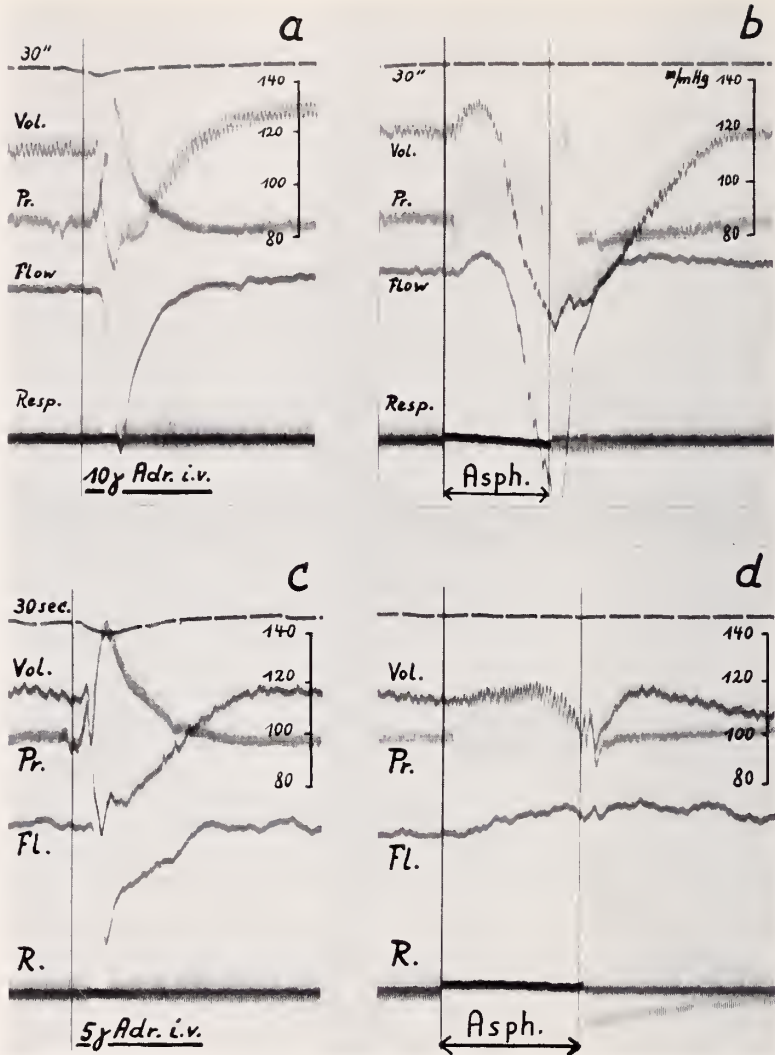


FIG. 7. Effect of clamping the main abdominal arteries on the reaction of kidney vessels to adrenalin and general asphyxia. By both procedures a decrease of kidney volume and renal blood flow results, as shown in the upper half of the picture (a, b). Shortly before the tests presented in section c and d were performed, the coeliac and mesenteric arteries and the lower abdominal aorta were ligated, producing an increase of the mean arterial blood pressure of 20 mm Hg without noticeable change of renal blood flow and kidney volume. As shown in c, the response to adrenalin remained unchanged with the exception that only half the dose is needed to produce a similar effect than before clamping of the abdominal vessels. In contrast to this even during a more prolonged tracheal occlusion there is no more decrease of blood flow or volume of the kidney, as shown in section d.

by the lung to renal vein determinations. This undoubtedly results from a retardation in the last part of the route which the blood takes on its way from the lungs to the renal vein. The time-values found before the injections averaged 10.7 seconds while those after injection averaged 19.1 seconds. It appears there-

fore, that the value for the circulation time of the isolated medullary blood circuit is higher than the integrated value for the flow velocity through the whole kidney. This seems to us to agree very well with the morphological findings: a rich supply of veins in the renal medulla, part of which possess only capillary walls.

In an india ink injected kidney, a well-filled venous system, particularly in the medulla and marginal zone, may give the appearance of a rich blood supply. On a purely morphological basis, however, this conclusion may not be warranted. Only moderate increases in venous pressure are required to present pictures of

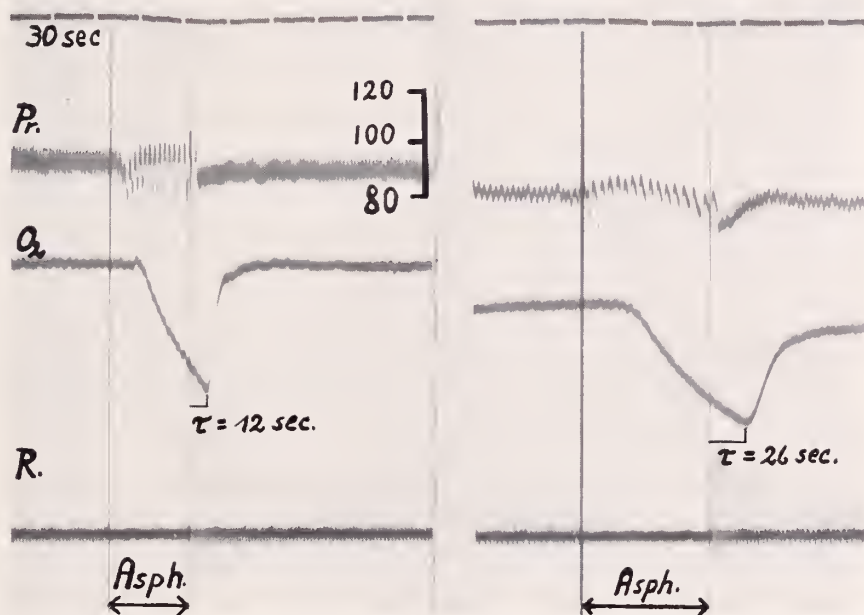


FIG. 8. Estimation of circulation-time lung to renal vein before and after blocking great parts of the cortical vessels of the kidney by glass beads. During clamping of the trachea the oxygen saturation of the renal venous blood starts to fall. This fall outlasts the re-opening of the trachea by 12 seconds, thus indicating the time the pulmonary blood needs to reach the renal vein. Repetition of the same test after the glass spheres have been injected in the kidney shows a time lag of 26 seconds between the first inspiration after asphyxia and the onset of increase of the O_2 -curve.

a highly filled medullary vascular bed, even if at the same time the arterial inflow is reduced. Thus it is possible that during many cases of epinephrine action or asphyxia, intrarenal india ink injection presents the picture of a widely different staining of cortical and medullary zones. This is a phenomenon that resembles a medullary bypass but which is attributable to venous congestion. This same factor is also responsible for the not too rare observation in india ink injected kidneys of venous backflow from the marginal zone into the interlobular veins and into great portions of the cortical capillaries in spite of the absence of any glomerular filling. We are, therefore, of the opinion that morphological evidence

for a renal blood diversion mechanism from cortex to medulla is relative and needs concomitant functional proof. The effects of epinephrine and asphyxia in our experiments do not present any proof for the existence of a medullary bypass mechanism in the rabbit kidney.

SUMMARY

In experiments on anesthetized rabbits two questions of general importance for renal hemodynamics have been investigated:

1. We employed the technique of intra-arterial injections of glass spheres (renal artery) in order to obtain evidence for the existence of *arteriovenous anastomoses* in the rabbit kidney. We failed in most cases to recover glass beads outside of the kidney. The behavior of renal blood flow and of O₂-saturation in the renal vein under the influence of these injections is such that it suggested the participation of arteriovenous short circuits.

2. Changes of kidney volume, of renal blood flow and of O₂-saturation in the renal vein, as produced by adrenalin injections or by asphyxiation of the animals, do not indicate any appreciable diversion of renal cortical blood through a *medullary bypass*. Moreover, the passage of blood through an isolated system of medullary vessels is slower than under normal conditions with irrigation of both cortex and medulla of the kidney.

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THE EFFECT OF HISTAMINE ON AN ISOLATED SYMPATHETIC GANGLION*

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There is good evidence that, under certain conditions, histamine can stimulate the cells of the suprarenal medulla to release epinephrine and, in the light of recent research, probably norepinephrine as well (1, 2, 3, 4, 5, 6). This is the reason why histamine is used as a diagnostic aid in suspected cases of pheochromocytoma (7, 8). Since the cells of the suprarenal medulla are modified nerve cells of the sympathetic system (9), the question arises as to whether histamine could exert an action on sympathetic ganglia as well. Feldberg & Vartiainen (10) have so far been unable to find that histamine has any effect on the isolated perfused superior cervical ganglion of the cat. However, they have not investigated whether histamine exerts any influence on the action of physiological or pharmacological stimulating agents of ganglionic cells, agents such as acetylcholine, choline, nicotine or potassium chloride. Since sympathetic ganglia are usually influenced in the same way as the adrenal medulla by the same pharmacological stimuli, e.g., nicotine (11, 12), lobeline (13, 14), morphine (15, 16) or atropine (17, 18), it seemed worthwhile to re-examine the action of histamine on a sympathetic ganglion. For this purpose, experiments were carried out on the perfused superior cervical ganglion of the cat.

METHOD

The experiments were performed on 22 cats weighing 2 to 5.8 kgm., under chloralose anaesthesia (0.08–0.1 gm./kgm. intraperitoneally). In the preparation and perfusion of the ganglion we followed the method introduced by Kibjakow (19) and later modified by other workers (20, 16). The perfusion fluid used was Locke solution (NaCl 0.9 per cent, KCl 0.02 per cent, CaCl_2 0.02 per cent, NaHCO_3 0.02 per cent, glucose 0.1 per cent), filtered through sintered glass and aerated with pure oxygen during the perfusion. A thermostatically controlled water-jacket was used to heat the fluid, which entered the ganglion through small branches of the common carotid artery and left it via the internal jugular vein or via the deeper vertebral vein. From 0.5 to 1.5 ml. of fluid passed through the ganglion per minute. As indicator of the ganglionic effects transmitted along the intact postganglionic fibers, the contraction of the nictitating membrane was recorded isotonicly.

Histamine dihydrochloride was injected very close to the ganglion either alone or in combination with ganglionic stimulators, i.e., acetylcholine (Roche), choline chloride, nicotine and KCl. In a few experiments physostigmine sulfate was added to the perfusion fluid (1:200,000).

In some experiments the superior cervical ganglion was denervated by the

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previous aseptic removal (2 to 8 weeks before the perfusion experiment) of about 1 cm. of the cervical sympathetic nerve.

RESULTS

As a rule, histamine alone given in single injections into the ganglion in doses ranging from 0.03 to 100 microgm. produced no detectable effect on the muscle

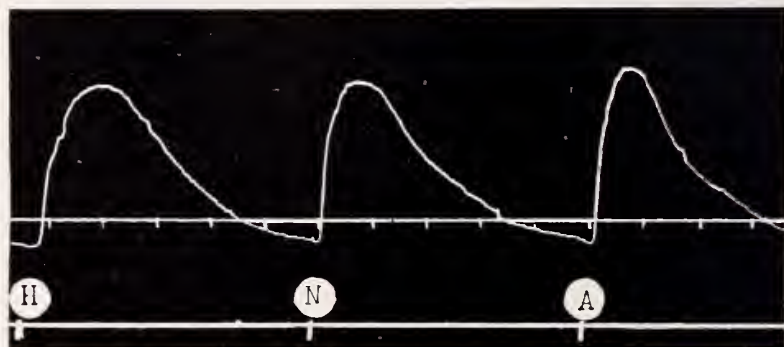


FIG. 1. Contractions of nictitating membrane during perfusion of denervated superior cervical ganglion (right) due to single injections of histamine (10 microgm. at H), nicotine (0.3 microgm. at N) and acetylcholine (1 microgm. at A). Time intervals: 1 minute.

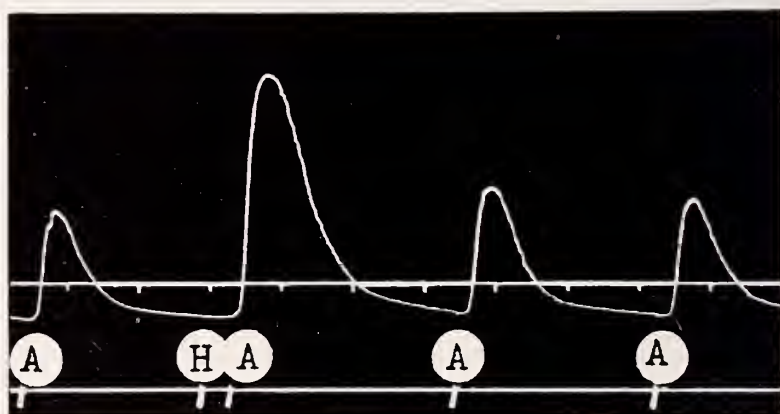


FIG. 2. Contractions of nictitating membrane during perfusion of normal superior cervical ganglion (right) due to single injections of acetylcholine (5 microgm. at A). Time intervals: 1 minute. Potentiating action of histamine (5 microgm. at H).

of the nictitating membrane. Only in four experiments out of 22—two on normal and two on denervated ganglia—did histamine (1 to 30 microgm.) produce contraction of the nictitating membrane (fig. 1).

However, when acetylcholine was given 30 seconds after histamine, the action of acetylcholine was usually (in 14 of 18 experiments) potentiated by pretreatment with histamine (fig. 2). Doses of histamine less than 1 microgm. were ineffective; potentiation was most evident when doses of 5 to 100 microgm. histamine were used (table 1).

By injecting acetylcholine at intervals of 3 minutes it was found that this potentiating effect of histamine on the action of acetylcholine was of very short duration (fig. 2). In most experiments, only the first injection of acetylcholine, given 30 seconds after injecting histamine, produced a greater response than normal, whereas subsequent injections of acetylcholine at 3 minute intervals again gave normal responses as before histamine. Occasionally, however, the maximum potentiating effect occurred 3 minutes after giving histamine. By repeat-

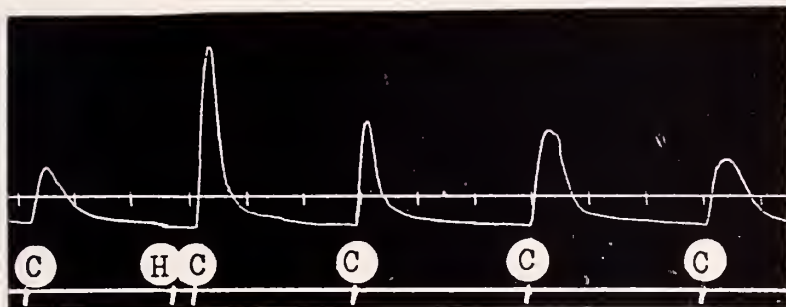


FIG. 3. Contractions of nictitating membrane during perfusion of normal superior cervical ganglion (right) due to single injections of choline (30 microgm. at C). Time intervals: minute. Potentiating effect of histamine (10 microgm. at H).

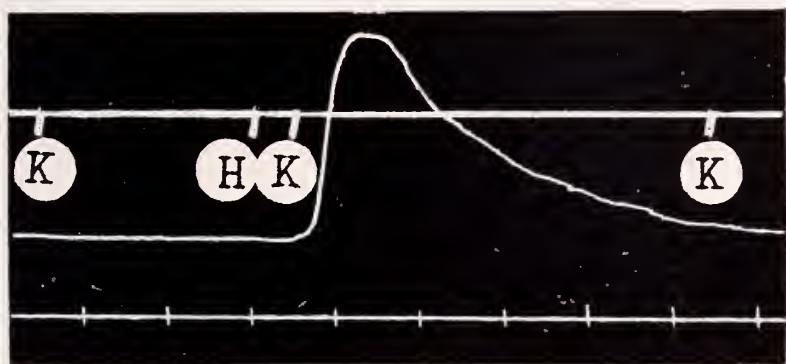


FIG. 4. Response of nictitating membrane during perfusion of normal superior cervical ganglion (right) to KCl (2 mgm. at K). The subthreshold dose of KCl becomes effective 30 seconds after histamine (50 microgm. at H). 5 minutes later 2 mgm. KCl again without effect. Time intervals: 1 minute.

ing the injection of histamine, the potentiation of the acetylcholine effect could often, but not always, be reproduced.

The ganglionic actions elicited by choline chloride (fig. 3) and KCl could also be potentiated by injection of 5 to 50 microgm. histamine 30 seconds beforehand. Potentiation was maximal about 30 seconds after the histamine had been given and then gradually decreased. Subthreshold doses of KCl became effective after pretreatment with histamine (fig. 4). The effect of nicotine on the ganglionic cells could likewise be potentiated by histamine (table 1).

On denervated ganglia histamine also produced a short-lasting increase in

the excitability to acetylcholine. However, the limited number of observations does not allow the conclusion to be drawn that in the denervated structure histamine would be more potent than in the normally innervated one.

We then endeavoured to determine whether antihistaminic substances would antagonize this potentiating effect of histamine. Since, in small doses, the antihistaminic drugs depress the action of acetylcholine on the ganglia, we have not yet been successful in finding a dose small enough to diminish the potentiating effect of histamine, without interfering with the action of acetylcholine.

TABLE 1

The potentiating effect of histamine on the action of acetylcholine, choline, KCl and nicotine on the isolated perfused superior cervical ganglion of the cat

EXPERIMENT	GANGLIONIC STIMULATING AGENT	DOSE INJECTED IN MICROGM.	HISTAMINE DIHYDRO- CHLORIDE INJECTED IN MICROGM.	MAXIMAL HEIGHT OF CONTRACTION OF THE NICITATING MEM- BRANE (IN MM.)		PER- CENTAGE INCREASE
				Before in- jection of histamine	After in- jection of histamine	
1	Acetylcholine	5	1	14	23	64
2 (denervated ganglion)	Acetylcholine	0.3	5	13	25	92
3	Acetylcholine	3	30	5	10	100
4	Acetylcholine	30	100	8	16	100
5	Choline	100	3	9	42	365
6	Choline	30	10	7	24	242
7	Choline	300	100	15	19	26
8 (denervated ganglion)	KCl	1000	5	4	34	750
9	KCl	600	10	11	26	136
10	Nicotine	0.3	3	10	23	130
11	Nicotine	0.3	5	14	31	120

DISCUSSION

When injected close to the isolated perfused superior cervical ganglion of the cat in doses of 1 to 100 microgm. histamine usually had no action of its own, i.e., it was not able to excite contraction of the nicitating membrane. In general we were able to confirm the results of Feldberg and Vartiainen (10), who found no direct action of histamine, although in our experiments histamine rarely produced contraction of the nicitating membrane. We are therefore of the opinion that histamine usually lacks the property of stimulating sympathetic ganglionic cells, but is not inherently unable to do so.

Histamine was observed to exert a sensitizing effect on the stimulating action of acetylcholine in about two thirds of our experiments. This action of histamine is related to effects exerted on the ganglionic cells or at the point of origin of the postganglionic fibers, or both, since it also occurs after denervation. It could be attributed partly to the anti-cholinesterase properties of histamine (21), since we observed no potentiation of the acetylcholine response during perfusion with physostigmine (1:200,000). Such an explanation, however, would not ac-

count for the potentiation of choline, KCl and nicotine. The sensitizing effect of histamine on the ganglionic cells is probably to some degree independent of its anti-cholinesterase activity.

These experiments demonstrate that, in the case of histamine, stimulation of the adrenal medulla corresponds with the increase in excitability of sympathetic ganglionic cells.

Since sympathetic ganglionic cells have many properties in common with the neuromuscular end plate, it may be of interest to note that histamine also increases the response to acetylcholine of the dorsal leech muscle (22) and of the frog rectus abdominis muscle (23).

SUMMARY

1) In the isolated perfused superior cervical ganglion of the cat (Kibjakow's method) histamine dihydrochloride in doses from 1 to 100 microgm. only rarely has the power to excite directly the response of the nictitating membrane.

2) In these dosages histamine usually augments the response of the innervated or denervated ganglion to acetylcholine, choline, nicotine and potassium chloride given immediately afterwards.

3) This action of histamine may be exerted either on the ganglionic cells or on the postganglionic fibers, and is probably only partly dependent upon the anti-cholinesterase activity of histamine.

4) The experiments demonstrate that in regard to histamine, too, the sympathetic ganglionic cells have many properties in common with the cells of the adrenal medulla.

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ÜBER ANGRIFFSPUNKT UND WIRKUNGSWEISE MORPHINÄHNLICH WIRKENDER ANALGETIKA*

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[Innsbruck]

Der Schmerz als warnende Reaktion auf zellschädigende Einflüsse einer feindlich gesinnten Umwelt ist eine entwicklungsgeschichtliche uralte Einrichtung; schon die negative Chemotaxis einzelliger Lebewesen könnte man ja als eine Urform der Schmerzreaktion ansehen. Beim höheren Tier ist der Schmerz zu dem viel komplizierteren Komplex eines nozizeptiven Reflexes weiterentwickelt worden, der nach Ebbecke (1, 2) "auch in seinem subjektiven Teil die Eigentümlichkeiten hat, die als Reflexgesetzmäßigkeiten aus den Untersuchungen am Spinaltier bekannt sind." Die auslösende Ursache ist auch beim höheren Tier wie beim Einzeller jedoch immer noch eine Zellschädigung bzw. eine dabei frei werdende chemische Substanz. Durch diese Verfeinerung des Mechanismus wird der Schmerz beim höheren Tier zur *Sinnesempfindung* erhoben. Daß er ein den anderen Sinnesempfindungen gleichzustellender und von der Tastempfindung getrennter, gewissermaßen sechster Sinn ist, geht aus den in der Literatur beschriebenen Fällen der menschlichen Pathologie hervor, in denen bei sonst voll erhaltenen Qualitäten des Tastsinnes die Schmerzempfindung vollkommen fehlte. (2-6)

Beim Menschen schließlich wird durch Entwicklung der sekundären Rindenfelder, vor allem des vorderen Stirnhirns, die einfache Sinnesempfindung des Schmerzes zum *Schmerzgefühl*, zum Schmerzerlebnis transformiert, das den Schmerz "von einem warnenden Freund zu einem oft sinnlos quälenden Feind gemacht hat" (Hoche(7)).

Trotz dieses großen Unterschiedes zwischen Mensch und Tier, der die experimentelle Forschung auf diesem Gebiet erschwert, wird im Mechanismus von Schmerzentstehung und Schmerzbekämpfung zwischen Mensch und Tier ein prinzipieller Unterschied nicht bestehen; sowohl die Unterdrückung der Schmerzreaktion des Tieres, wie auch des Schmerzerlebnisses beim Menschen besteht in der Unterbrechung dieses Reflexbogens—allerdings auf verschiedenen Ebenen der Schmerzbahn. Auf letzterem Umstand beruhen auch die weit auseinander liegenden Dosen für die Unterbrechung der subcortikalen Schmerzreaktion am Tier und für die klinische Analgesie beim Menschen. Diese besteht ja im Prinzip nur aus einer Reduktion des *Schmerz-gefühls* zur *Schmerzempfindung*, führt also gewissermaßen den Menschen gegenüber dem Schmerzreiz auf die Stufe des Tieres zurück.

Wenn man den Angriffspunkt der pharmakodynamischen Analgesie finden will, dann muß man sich zunächst über die Elemente im klaren sein, aus denen sich dieser Schmerzreflex aufbaut. Wie jeder reflektorische Vorgang besteht auch der Komplex des Schmerzes aus einem peripheren Reizempfänger, einer

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afferenten Bahn, einer oder mehreren Schaltstellen und den von dort ausgehenden efferenten Bahnen, die nun entweder zurück zur Peripherie ziehend die Schmerzreaktion auslösen, oder weiter zentralwärts laufend schließlich das Schmerzerlebnis als Endeffekt vermitteln.

Die Beantwortung der Frage, welches dieser Elemente der Angriffspunkt der Analgetika ist, wäre wesentlich leichter, wenn wir ein Modell zum Studium solcher Vorgänge hätten, das einfacher zu durchschauen wäre als die durch allerhand unkontrollierbare Umstände beeinflussbare Schmerzreaktion des ganzen Tieres.

Ein solches Modell ist der Peristaltikreflex des Darmes, der sich nach der Methode von Trendelenburg (8) oder einer ihrer Modifikationen auch am isolierten Darm studieren läßt. Dies hat, wie bei allen mit isolierten Organen arbeitenden Methoden den großen Vorteil, von allen am Ganztier störenden Nebenwirkungen, vor allem solcher zentraler Genese, unabhängig zu sein. Der auslösende Reiz ist hier der Dehnungsreiz, der über die Ganglienkette des Auerbachschen Plexus schließlich zur "Reaktion", der peristaltischen Kontraktionswelle führt.

Schon Trendelenburg hatte gefunden, daß dieser Reflex bereits durch außerordentlich kleine Dosen von Morphin reversibel unterdrückt wird. Wie Versuche (9) mit den neuen synthetischen Analgetica der Phenylpiperidin-(Pethidin-) (10, 11), Diphenylmethan-(Methadon-) (12) und Morphinan-Klasse (13, 14) zeigten, ist diese Wirkung außerdem für morphinähnlich wirkende Analgetika spezifisch, d.h. sie geht mit der analgetischen Wirksamkeit parallel. Dies konnte nicht nur bei konstitutionell verschiedenen Verbindungen, sondern auch bei den optischen Isomeren der gleichen Verbindung gezeigt werden. So ist z.B. die d-Form des 2-Dimethylamino-4,4-diphenylheptanon (5) (Methadon, Polamidon) oder des 3-Oxymorphinan (Dromoran) etwa 10–20 mal weniger wirksam auf die Peristaltik als die entsprechenden 1-Verbindungen, wie es auch bereits bezüglich der analgetischen Wirksamkeit bekannt war (15).

Der Angriffspunkt dieser spezifischen peristaltischen Wirkung liegt nicht peripher beim Übergang der efferenten Reflexbahn zum Erfolgsorgan. Dies ergibt sich aus dem Unterschied der Wirkungsweise gegenüber dem ebenfalls peristaltikhemmenden Atropin. Beim peripher angreifenden Atropin ist die peristaltikhemmende Konzentration von der gleichen Größenordnung wie diejenige, welche die direkte Azetylcholinwirkung aufhebt. Die Analgetika dagegen sind gegen Acetylcholin teils vollkommen unwirksam, wie Morphin oder die Morphinane, teils werden Konzentrationen benötigt, die bis zu tausendmal höher sind als die zur Peristaltikhemmung nötigen.

Auch eine Unterbrechung der afferenten oder efferenten Leitungsbahnen kommt nicht in Frage, da die Analgetika zwar, wie z.B. Pethidin (Dolantin) oder Methadon (Polamidon) eine gewisse lokalanästhetische Wirksamkeit besitzen können, aber nicht müssen (15–17). So sind z.B. Morphin oder das 3-Oxymorphinan lokalanästhetisch unwirksam. Auch in dieser Beziehung besteht somit keinerlei Parallelität, weder mit der peristaltikhemmenden, noch mit der analgetischen Wirksamkeit.

Daß die Peristaltikhemmung nichts mit der gegen einen abnorm erhöhten Muskeltonus gerichteten "spasmolytischen" Wirkung zu tun hat, die viele der synthetischen Analgetika—wenigstens am isolierten Darm—zeigen, ergibt sich daraus, daß auch in dieser Beziehung keinerlei Parallelität mit der analgetischen Wirksamkeit besteht. So sind die optischen Isomeren spasmolytisch gleich wirksam (15) und dem Morphin sowiedem Oxymorphan (9) fehlt auch diese Wirkung vollkommen. Schließlich sind die für eine "Spasmolyse" nötigen Konzentrationen um einige Zehnerpotenzen höher als bei der Peristaltikhemmung, die unter Umständen noch bei Konzentrationen von 1:100 Millionen und darunter nachweisbar ist.

Der Angriffspunkt für die Hemmung der Peristaltik dürfte daher mit größter Wahrscheinlichkeit in den Ganglien zu suchen sein, durch deren Vermittlung der afferente Dehnungsreiz die peristaltische Reaktion auslöst.

Diese Ergebnisse an dem relativ einfachen und leichter analysierbaren Mechanismus der Peristaltikhemmung können die Annahme stützen, auch für die analgetische Wirkung den Angriffspunkt in entsprechende Schaltstellen der Schmerzbahn zu verlegen, in denen unter der Wirkung der Analgetika der von der Peripherie kommende Schmerzreiz entweder gar nicht oder doch nur abgeschwächt auf die efferenten Bahnen übergeleitet wird.

Zu dem gleichen Schluß wird man bei direkter Analyse der analgetischen Wirkung—so weit sie möglich ist—gedrängt. Peripher am Ursprungsort des Schmerzreizes können die Analgetika nicht angreifen, denn sonst müßten Schmerzreaktion und Schmerzgefühl durch die gleiche Dosierung aufgehoben werden, was ja in keiner Weise der Fall ist. Die Leitungsbahnen können beim Schmerzreflex aus den gleichen Gründen wie beim Peristaltikreflex auch nicht der Angriffspunkt sein. Schließlich kann der Angriffspunkt auch nicht—oder zumindest nicht allein—im Großhirn liegen, da ja der Pseudoschmerzreflex des großhirnlosen Tieres ebenfalls zu unterdrücken ist. Außerdem haben die bewundernswerten Versuche einiger Autoren (18–21), vor allem von Wikler (22–26) und seinen Mitarbeitern am Spinaltier gezeigt, daß selbst hier noch eine Unterbrechung nociceptiver Reizreflexe bei entsprechend gesteigerter Dosis durch Morphin und morphinähnliche Analgetika möglich ist. Die Tatsache, daß hier vor allem multineuronale Reflexe durch die Analgetika beeinflußt werden, haben zu dem Schluß (25, 26) geführt, daß ihr Angriffspunkt in "internuntial neurons" zu suchen ist.

Die Annahme, daß "Zwischenneurone"—oder vielleicht besser und präziser ausgedrückt—die mit der Verstärkung und Fortleitung des ankommenden Reizes in den Schaltstellen der Schmerzbahn verknüpften chemischen Vorgänge der Angriffspunkt der morphinähnlich wirkenden Analgetika sind, könnte noch für eine andere Eigentümlichkeit dieser pharmakodynamischen Wirkung eine Erklärungsmöglichkeit bieten, daß man nämlich umso kleinere Dosen zur Wirkungsentfaltung braucht, je weiter zentralwärts die Unterbrechung der Schmerzleitung erfolgt. Man spricht in diesem Zusammenhang gerne von einer "zentralwärts zunehmenden Empfindlichkeit" der nervösen Elemente, ausgehend von der Ansicht, daß phylogenetisch jüngere Erwerbungen weniger widerstands-

fähig gegen äußere Einflüsse sind. Dies widerspricht jedoch nicht nur dem Bauplan der Natur, die im Zuge der Fortentwicklung wohl *aus*baut, aber nicht *um*-baut, es widerspricht auch der Tatsache, daß nach klinischer Erfahrung gerade Thalamusschmerzen auch durch die höchsten therapeutisch anwendbaren Dosen der Analgetika kaum zu beeinflussen sind, obwohl hier der Angriffspunkt hoch oben im Zentralnervensystem liegen müßte.

Viel näherliegend wäre die einfache Annahme, daß die zentralwärts zunehmende "Empfindlichkeit" nur scheinbar und in Wirklichkeit nichts anderes ist, als die Summation von Einzelwirkungen auf die hintereinander geschalteten Schaltstellen. Eine pharmakodynamische Schwächung der Reizübertragung wird sich an allen Schaltstellen in gleicher Weise auswirken, gleichgültig, ob sie mehr peripher oder mehr zentral gelegen sind, und eine an sich geringe Hemmung wird den Schmerzreiz nach Durchlaufen mehrerer Schaltstellen durch Summation der Einzelwirkungen schließlich unterschwellig machen. Für die Hemmung fermentgesteuerter chemischer Reaktionen gibt es ja kein "Alles-oder-Nichts-gesetz"; ihr Ausmaß ist von der Konzentration des hemmenden Stoffes abhängig. Mit anderen Worten: Je mehr Schaltstellen zwischen auslösendem Reiz und Endeffekt liegen, desto kleinere Dosen sind zu seiner Unterdrückung notwendig. Daher auch die überaus große "Empfindlichkeit" des Peristaltikreflexes mit seinen zahlreichen Neuronen und die gegenüber der klinischen Analgesie relativ großen Dosen, die zur Unterdrückung der unbewußten Schmerzreaktion am Mittelhirn oder gar Spinaltiefer benötigt werden.

Eine Erforschung des der Schwächung der Reizübertragung zugrunde liegenden fermentgesteuerten chemischen Prozesses wird so lange ein Tappen im Dunklen bleiben, solange nicht dieser Prozeß selbst erforscht ist. Wohl haben Versuche (27-30) gezeigt, daß sich Fermente durch die morphinähnlich wirkenden Analgetika hemmen lassen. Aber diese Fermenthemmung ließ sich einerseits bei fast allen bisher untersuchten Fermenten nachweisen, andererseits sind dazu so hohe Konzentrationen nötig, daß von einer Spezifität keineswegs gesprochen werden kann. Dies umso weniger, als sich in den bisherigen Versuchen keine Parallelität zwischen Fermenthemmung und analgetischer Wirksamkeit ergab. So wird z.B. die Hefegärung durch die optischen Isomeren des Methadon oder Oxymorphan in gleicher Weise gehemmt.

ZUSAMMENFASSUNG

Die Unterbrechung des Peristaltikreflexes am isolierten Darm ist für die morphinähnlich wirkenden Analgetika spezifisch und ein brauchbares einfaches Modell zum Studium von Angriffspunkt und Wirkungsmechanismus solcher Verbindungen.

Es wird zu begründen versucht, daß der primäre Angriffspunkt dieser Verbindungen in den in die Schmerzbahn eingebauten Schaltstellen bzw. den dort mit der Reizübertragung verbundenen chemischen Vorgängen zu suchen ist und daß die zentralwärts zunehmende Empfindlichkeit nur scheinbar und nur eine Summation von submaximalen Einzelwirkungen auf diese Schaltstellen ist.

SUMMARY

Morphine and similar analgetic drugs interrupt in a specific way the reflex peristalsis of an isolated segment of intestine (Trendelenburg). This object is therefore a simple and useful tool to study the mechanism of morphine and related compounds.

An attempt is made to demonstrate that morphine and similar agents act primarily on the chemical reactions of the synaptic transmissions of the pain reflex. The increase in susceptibility to morphine and related drugs when tested on higher stations of the pathway for pain is apparent only rather than real and explained by the action of the drug on internuncial synapses (Wikler). Subliminal poisoning of each synapse will thus become evident by simple summation.

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"NICOTINIC ACTIVITY" AND THE PROBLEM OF PHARMACOLOGIC SELECTIVITY*

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I

When on his 80th anniversary he looks back upon the development of scientific thought in his special field, Professor E. P. Pick, who early in his distinguished career turned from immunology to pharmacology, will acknowledge with particular indulgence the timeliness of a brief discourse on pharmacologic selectivity. The two branches of science which were enriched by E. P. Pick's work can well serve to delineate selectivity from specificity, the term often indiscriminately employed in its place. "Specificity," as the word implies, is intrinsically a quality and can be applied very aptly to the action of immunologic agents, each of which aims exclusively at a different "specific" target. In contrast, "selectivity," an attribute of pharmacologic action, is exquisitely a quantity. The famous old maxim of pharmacology‡ can well be changed into: "*Dosis sola facit selectivitatem*." To rely on a drug's unconditional selectivity, to confound selectivity and specificity or to consider drugs as "*specifica*" sooner or later results in disappointment. On the other hand, every type of selectivity, because of the quantitative limitations of all selective phenomena, is liable to be subject to re-interpretation and subdivision.

The features inherent in the conception of selectivity will here be expounded by the example of the "nicotinic action" of drugs. This term (14) has more and more been applied to designate the entirety of pharmacologic actions on autonomic synapses, muscular and ganglionic, to which latter the present discussion will be focussed. The unitarian implications of such an application have been favored by the apparent intrinsic intertwinement of all kinds of autonomic ganglionic activity in nicotine itself (13). The possibility of factual dissociation of the complex of "nicotinic activity" became evident only during the last lustrium, when tetraethylammonium was definitely established as a selectively ganglion-depressant agent (1, 2), when certain findings (16) seemed to point to a comparative selectivity of pentamethonium for depression of sympathetic ganglia, and when certain cresylphenoxcholines were found to have remarkable selectivity for stimulation of sympathetic ganglia (11).

With such tools at hand, an approach could be made to some of the problems of selectivity by comparing different nicotinic drugs for their patterns of autonomic ganglionic actions,—the elements of which patterns are visualized in

* Extension of parts of a paper given at the 36th Meeting of the Federation of American Societies for Experimental Biology, Atlantic City, 1950 (cf. (11)). The experiments reported here were supported in part by a grant from Life Insurance Medical Research Fund.

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‡ "*Dosis sola facit venenum*".

Figure 1. The various potency data obtained in the four "quadrants" of activity were correlated with some complementary data adapted from the literature. Neither the adaptations nor the correlations were possible without certain more or less arbitrary assumptions. Thus, whereas the values obtained experimentally have the validity of all experimental data, i.e., are valid under the observed experimental conditions, the values arrived at by integration are devoid of any claim to standard validity; but this is not believed to detract from their usefulness in the general purpose of this study, which is to illustrate concepts rather than to submit numerical data.

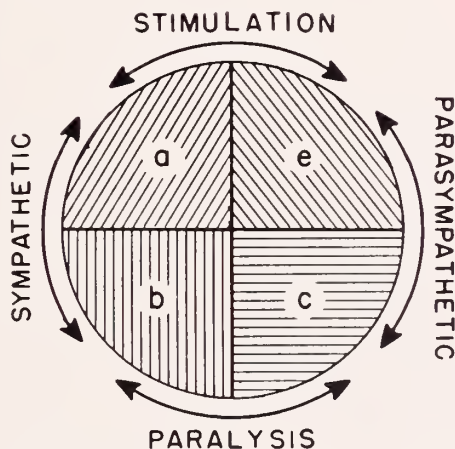


FIG. 1. The four quadrants of autonomic ganglionic selectivity

Mnemonotechnic note: The first two letters of the alphabet (a, b) were chosen as symbols for activity at sympathetic, two subsequent letters (c, c) as symbols for activity at parasympathetic ganglia; vowels to designate ganglion stimulation, consonants to designate depression.

II

Experimental Procedures. Parasympathetic ganglionic activity was measured in the excised guinea pig ileum tube preparation devised by Trendelenburg (19) for the study of the peristaltic reflex response to increased intraluminal hydrostatic pressure. Since the intramural ganglia concerned in this peristaltic reflex are practically completely parasympathetic, Feldberg and Lin (5) introduced the preparation for determining parasympatho-gangliolytic drug activity. In the present work it was found that the preparation is also a useful test object for studying stimulant actions on these ganglia; parasympathetic ganglion-stimulant drugs decrease measurably the threshold of the intramural reflex when the intraluminal pressure increase is appropriately synchronized with the addition of the test drug to the bath fluid. Potencies for stimulant and depressant actions were expressed by E.C.₅₀, i.e., that concentration of the drug in the bath fluid which, in 50% of experiments, decreased (stimulation) or increased (depression) the pressure threshold by 33%.

Sympathetic ganglionic stimulation was measured in the atropinized (0.5 mg/kg) cat under pentobarbital anesthesia, and potency was expressed by the intravenous dose of the test drug producing a blood pressure rise of 50 mm Hg. Sympathetic ganglionic depression was measured in the same preparation by determining the intravenous dose of the test drug

which decreased by 50% the pressor effect of a moderately effective, subsequently injected dose of the ganglion-stimulant drug, *o*-(*p*'-fluorobenzyl)-phenoxycholine (Bl-244). The effective doses calculated for both of these endpoints are averages from at least six tests.

Substances. The six substances studied were: (1) hexamethonium (C6), (2) pentamethonium (C5), (3) tetraethylammonium (TEA), (4) *o*-(*p*'-fluorobenzyl)-phenoxycholine (Bl-244), (5) phenoxycholine (PhCh), the parent substance of Bl-244 (9) and (6) nicotine.*

Evaluation Procedures. Relative potencies (RP; specified as RP_a , RP_b , RP_c and RP_e) of the test drugs (T) were determined for each of their four ganglionic actions *a*, *b*, *c* and *e* (see Figure 1) from the equieffective doses (*D*) or concentrations (*c*), one of the drugs (*S*) being used as the standard of reference ($RP = D_s/D_T$, or $RP = C_s/C_T$). In all four series of RP, PhCh was used as the standard of reference (*S*) because of its unambiguous activity in all four quadrants of ganglionic action. A few RPs (for C6 and TEA), not measured experimentally, were estimated from literature data; this was possible for RP_c on the basis of the potency ratios obtained on the intestinal ganglia by Paton and Zaimis (16), and for RP_e on the basis of the wide agreement about the lack of ganglionic stimulant actions at even high dosage levels of the two drugs (15, 14, compare however below, Section III). For RP_b of C6 and TEA, the potency ratios determined on the superior cervical ganglion (Paton and Zaimis, 16) were employed. Values based on such indirect estimates will be marked by *italics*. For more extended comparisons, the interrelationship of the four series of potency data had to be considered. Whereas the series *a* and *b* are mutually directly referable, being obtained under equal experimental conditions and measured in equal dimensions, and whereas the same holds true for the series *c* and *e*, the common denominator between these two pairs of series, required for conversion of the RP values of all four series into *P*-values referred to one common standard, is difficult to find. The scanty literature data leave no choice but to introduce certain assumptions. According to simultaneous experiments in the same individual animals, the blockade of transmission of electrically evoked impulses through the parasympathetic ciliary ganglion to the pupillary sphincter requires four times the TEA dose needed for that through the superior cervical ganglion to the pupillary dilator (12). By employing this potency ratio of 4 as the basis of the correction factor for the RP_b series, the four *P*-series were calculated, all *P*-values being uniformly referred to P_c of PhCh as standard.

The *activity type* of the individual drug was then expressed by enumerating those of the four actions, which were found embodied in the drug, in terms of their symbols, *a*, *b*, *c* or *e* and in the order of descending potencies *P*. In the resulting expressions, such as "(*b,c*)" or "(*a,b,e,c*)", the first-named action is the most selective action of the drug concerned, being characterized by the highest potency; the second action is more selective than the third one, and similar considerations apply to each subsequently enumerated action. Hence the terms *primary*, *secondary*, etc. *selectivity* were introduced and their *level* (s.: of *selectivity*) in the individual drug was correspondingly designated (I, II, III, etc.).

The *degree of selectivity* (*D.S.*) of any action of a drug was roughly expressed by the potency ratio between this action and the action on the next-lower level (or in instances, for special comparisons, an action on any appropriate lower level). *D.S.*, thus, is an index which characterizes the range in which the drug displays the activity concerned (in the numerator of potency ratio) without interference of the lower-level activity referred to (in the denominator).

Comparative selectivity (*S.R.*), the ratio between comparable *D.S.*-values of different drugs in reference to the drug of lowest *D.S.* in the group, was employed to compare drugs with each other with regard to the range of selectivity of an action they have in common.

III

Tables 1 to 4 present the results of an application of the above outlined procedures to the complex of autonomic ganglionic activity of nicotinic drugs. None

* For 1 and 2, we are indebted to Dr. E. J. de Beer, Wellcome Research Laboratories, Tuckahoe, N. Y.; for 4 and 5, to Dr. A. Menotti, Bristol Laboratories, Inc., Syracuse, N. Y.

of the six drugs studied is limited in its ganglionic activity to a single action, but each one has a composite action type (see Table 3). When only the most selective action, that of highest potency in the individual drug (Table 1,B), is considered, only two out of four possible groups are found represented, three of the drugs embodying sympathoganglionic stimulant, the other three sympathoganglionic depressant activity. According to the entire patterns of ganglionic activity em-

TABLE 1
*Equivectiveness and potency values of 6 nicotinic drugs for the four ganglionic activities**

GANGLIONIC ACTION	C6	C5	TEA	BL-244	PhCh	NICOTINE
A. Equieffective Doses and Concentrations						
(a) Sympath. Stimulation ($\mu\text{g/kg}$).....	>20000	>20000	>20000	10	7	10
(b) Sympath. Depression ($\mu\text{g/kg}$).....	400	500	4000	650	200	800
(c) Parasymp. Depression ($\mu\text{g/10cc}$).....	3.0	10	70	67	116	27
(e) Parasymp. Stimulation ($\mu\text{g/10cc}$).....	>10000	>10000	>10000	>10000	6	15
B. Potencies, referred to P _c of PhCh						
(a) Sympath. Stimulation.....	<1.3	<1.3	<1.3	2700	3900	2700
(b) Sympath. Depression.....	67	53	6.6	41.0	133.0	33
(c) Parasymp. Depression.....	38.7	11.6	1.7	1.7	1.0	4.3
(e) Parasymp. Stimulation.....	<0.012	<0.012	<0.012	<0.012	19.3	7.7

* Italicized numbers designate values obtained indirectly by conversion from the literature data quoted in the text (Evaluation Procedures). For further details compare text.

TABLE 2
Potency ratios
(Degree of relative selectivity, D.S.)

1	2	3	4	5	6	7	8	9	10
	a/b	(b/a)	a/c	c/a	a/e	b/c	b/e	(c/e)	e/c
C6	—	(>50)	—	(>29)	—	1.7	>5550	(>3230)	—
C5	—	(>40)	—	(>9)	—	4.6	>4430	(>966)	—
TEA	—	(>20)	—	(>5)	—	4.0	>550	(>138)	—
BL-244	65	—	1540	—	>22000	23.7	>3420	(>144)	—
PhCh	29	—	3860	—	200	133.0	7	—	19.3
Nicotine	80	—	855	—	346	7.8	4.3	—	1.8

bodied, C5, C6 and TEA represent one type, nicotine and PhCh another, and BL-244 a third.

The drugs differ furthermore according to the degree of selectivity (D.S.) associated with the different components of the activity pattern. The range of highest selectivity is not always the one in which an action has the widest margin of non-interference by the action of next-lower selectivity. For instance, the range of primary selectivity of the sympathoganglionic stimulant action of BL-244, nicotine and PhCh (A; see Table 3, column 1) is much wider than that of the

primary sympathogangliolytic selectivity of C5, C6 and TEA (b; column 7). Still greater is the D.S. of sympathetic over parasympathetic ganglion-stimulant action in the primarily sympathoganglionic stimulant group of Bl.-244, PhCh and nicotine (a, c; column 6), and the widest range of selectivity is, in two of them, the range between sympathoganglionic stimulant and parasympathoganglionic depressent activity (a, c, column 4, PhCh and nicotine).

TABLE 3
Selectivity type according to gradation of activities

DRUG	C6	C5	TEA	BL.-244	PhCh	NICOTINE
Type	b, c,	b, c,	b, c,	a, b, c	a, b, c, c	a, b, e, c
Level	I, II,	I, II,	I, II,	I, II, III	I, II, III, IV	I, II, III, IV

TABLE 4
Comparative selectivities (S.R.) of various nicotinic drugs
(Comparative potency ratios of different drugs on various selectivity levels)

1	2	3	4	5	6
Curr. Nr.	Activity	Level	Activity range covered	Drugs (in sequence of their S.R.s)	S.R. (Comparative selectivity)
1	a	I	a/b	Nicotine > Bl.-244 > PhCh	2.4 : 1.4 : 1
2	b	I	b/c	C5 > TEA > C6	2.7 : 2.3 : 1
3	c	II	c/a	C6; C5; TEA	(> 29; > 8.7; > 5.0)
4	e	III	e/c	PhCh > nicotine	10.8 : 1
5	b	I, II, II + III or II to IV	b/c	PhCh > Bl.-244 > nicotine > C6	77 : 14 : 4.5 : 1
6	a	I to IV	a/c	PhCh > Bl.-244 > nicotine	2.5 : 1.8 : 1
7	a	I to III	a/e	Bl.-244 > nicotine > PhCh	> 110 : 17 : 1
8	b	I to III, II to III or II to IV	b/e	C6; C5; Bl.-244; TEA; PhCh > nicotine	> 130; > 103; > 80; > 13; 1.6 : 1

On the other hand, the S.R. values, which are a measure of the comparative selectivity of the same action in different drugs (Table 4), show that substances may not differ greatly in a range in which they all exhibit high selectivity (expressed by D.S.). For instance, this comparative index, S.R., does not exceed 2.4 in any of the substances for the margin between stimulation and depression of sympathetic ganglia (Table 4, line 1), whereas for that between stimulation and depression of parasympathetic ganglia it can amount to 10.8 (line 4). How high, on the other hand, such indices can be, is indicated in the margin between sympathetic and parasympathetic ganglionic stimulation, where in one of the substances S.R. is higher than 115, and in the margin between sympathetic and parasympathetic ganglionic depression, in which the highest S.R. is 77.

IV

This study might be called a tentative exercise in quantitative spectrum analysis of the activity of nicotinic drugs; *viz.*, in terms of the light spectrum, an attempt to sample the absolute and relative intensity of one, more or less characteristic band in each of the four ranges of the autonomic ganglionic spectrum of a group of drugs. Indeed, the comparison with optical physics can go a long way. It is true the abscissa of the pharmacologic spectrum can as yet not be based on a systematic gradation like that of wave lengths; moreover, its study is necessarily eclectic because of physiological and methodological difficulties and shortcomings. One has therefore to be satisfied with measuring absolute intensities only at certain points (= "wave lengths" = actions) of a drug's presumably continuous spectral curve.

In pharmacology, potency is the equivalent of intensity. A drug with a strictly "one-band spectrum" would have only one steep spike in a narrow wave-length range, *i.e.*, real specificity. That the pharmacologic agents have complex patterns of activity,—as is confirmed by the characterization of the six drugs of the present study,—means that they have a spectral curve with more or less numerous elevations at different "wave lengths," each elevation differing from the other in height. It is here that the concept of selectivity is needed. The ratio in which one of the several peaks of intensity exceeds in height the next-highest is the Degree of Selectivity. The greater this ratio, the deeper is the drop from the former to the latter peak of the curve, hence the wider the range in which the drug can display its more selective action without interference by the next-selective action. For comparisons between the degrees of selectivity of different drugs in the same action, the Comparative Selectivity (= selectivity ratio = S.R.) which refers, so to say, the excess intensities of the same band in different substances to that of the one with the least excess intensity, is obviously helpful, and often more so than direct intensity comparisons between different substances.

The concepts of Selectivity and of Degree of Selectivity are by no means new; they have long been recognized as important criteria of the action spectrum of drugs. This is best emphasized by recalling the following situation: If all actions of a drug except that of highest selectivity are undesirable because they produce side-effects and/or toxic effects, the D.S. of the most selective action expresses the margin of safety of the drug (rather one of the many margins of safety, there being as many as there are side-actions). D.S. is then nothing else but the *Therapeutic Index* of the drug. This will explain why the evaluations in Tables 3 and 4 were not restricted to the uppermost range of the spectral curves, and why D.S. and S.R. were also calculated for lower levels of selectivity and even for ranges extending over several levels. D.S. values for such lower or aggregate levels acquire importance if the highest-selective action of a drug is undesirable but causes relatively negligible side-effects and a therapeutically greatly desirable action of the same drug is less selective, or if only a really severe side-effect from a lower selectivity level determines the limit of therapeutic usefulness of the drug.

Compared with the general significance of these considerations of spectrum analysis for which the examples presented offer unquestionably welcome illustra-

tions, the validity of the details of the examples is definitely limited, as has been emphasized in an introductory section. Not only some individual values, but also the entire qualitative and quantitative pattern may have to be revised with the aid of future, more arduous and extensive work.

Data (Stone, Entwisle and Loew, 18) which became accessible only after the conclusion of this paper may give an example of such a metamorphosis. They demonstrate the embodiment of sympathoganglionic stimulant activity in TEA, which adds (a) as a new component to the pattern of the drug; the action appears to be limited to the adrenal medulla (in essence, a sympathetic ganglion) and could only be demonstrated by means of local administration of TEA (0.5–4 mg) to this site. In a similar study of the vascular pressor effect of Bl-244 (11), which is also induced by sympathoganglionic stimulation but is only to about 50% due to adreno-medullary secretion (10), small fractions of a microgram applied locally were equieffective to 10 to 50 $\mu\text{g/kg}$ injected intravenously, quite in agreement with the enormously small perfusion doses in which nicotine stimulates the superior cervical ganglion (6). On the assumption of a similar ratio between the locally effective and the systemically equieffective dose, TEA has a P_a of 0.33 (*cf.* Table 1,B), a D.S. of 20 for b/a and of 5 for c/a (*cf.* Table 2). Its activity type changes from (b,c) to (b,c,a), a type not otherwise represented in our drug series, with a wide range of selectivity of (b) over (a).

Although the revision of the action pattern of TEA increases to four the number of action types represented in our series, this is only a small selection from the many possible types of nicotinic activity. It has been pointed out previously (11) that mere consideration of the possible qualitative combinations of the four activities leads to 15 types. If one considers the many more permutative and combinative variations which become possible by reversal of potency ratios (e.g. a/c *vs.* c/a) superficial estimate can readily reveal more than 30 possible types. The occurrence of drugs embodying other types might be seen indicated in the literature, at least in such faint outlines as the incompleteness of data allows to be recognized.

The most serious shortcomings of quantitations of the spectra of ganglionic drugs are not due to the inadequacy of conversion or integration factors, but to the eclectic nature of the test functions. None of the activities tested—and, for that matter, no single activity at all—can be adequately representative of the entire quadrant of ganglionic activity, of which it is a component. The various ganglia of the same division of the autonomic system differ in their sensitivity to the same drug, and the order of selectivities for different ganglia within the same division differs from drug to drug.

To give only a few examples: The degrees of selectivity of TEA for sympathetic as compared with parasympathetic ganglionic blockade (b/c) differ greatly according to the test ganglia employed (7, 16). When measured in terms of blood pressure effect, the sympathoganglionic depressant potency of C6 is smaller, that of TEA greater than when measured in terms of blockade of ganglionic transmission to the nictitating membrane (16), whereas the two ganglionic stimulants dimethylphenylpiperazinium and Bl-244 are more potent in terms of pressor than in terms of nictitating-membrane effect (10, 3). The autonomic angionic activity type of *d*-tubocurarine [above summarily reported as (c,b)] varies with the sympathetic ganglion tested (8).

Paton and Zaimis, to whom so much elucidation of the pharmacology of ganglionic synapses is owed, have already emphasized that greater knowledge of graded selectivity may result in the development of drugs with therapeutically desirable selectivity for only a certain part of a ganglionic system (16). Paton and Perry (17) discovered that ganglionic drugs differ in the basic mechanism of their ganglionic action; nicotine and tetramethylammonium act like acetylcholine in that they depolarize the ganglion cell membrane, whereas C6 and TEA act like curare in that they raise the threshold to the excitatory action of acetylcholine. This discovery may point the way to an understanding of the mechanisms governing the phenomenon of graded selectivities of the ganglionic drugs. Differences in accessibility of the loci of action, differences in the metabolic fate of the drug at these sites, and differences in the chemical structure of the receptors may also play their part in the phenomenon. The problem of the mechanisms involved is beyond the frame of this discussion. Merely on the basis of the phenomena analyzed, the present study serves to exemplify the dissolution of nicotinic ganglionic drug activity into the great variety of activity types originating from the varying degrees of selectivity of the components of the action spectra of the individual drug, and to emphasize the necessity of determining separately the selectivity of every single component (*cf.* also 16, 14). Thus, this discussion is an illustration of the "first principle of biodynamics," hinted at in Goethe's verse:

Nature has neither core nor shell,
She's both of it in the same spell,*

—Nature's principle to proceed always in the extrinsically most complicated manner as the only possibility of fulfilling her highly complex tasks with intrinsically greatest economy. Drugs are tracers of Nature's *modus operandi*; to comprehend their mechanism of action means to perceive her economic simplicity behind the perturbing exuberance of pharmacologic phenomena.

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* "Natur hat weder Kern noch Schale,
Beides ist sie mit einemale."

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RESISTANCE TO GRAFTING WITH LYMPHOSARCOMA CELLS IN RATS INJECTED WITH HOMOLOGOUS LYMPHOID CELLS*

H. C. STOERK, TATIANA BUDZILOVICH AND T. C. BIELINSKI

The reticuloendothelial system (R.E.S.) and especially splenic tissue have often been assumed to exert an action antagonistic to neoplastic cells. Observations relevant to this possibility have been critically reviewed by Stern and Wilhelm (1). More than 40 years ago it was observed by Apolant (2) that splenectomy facilitated the grafting of tumor tissue. It appears now well documented that procedures leading to a diminution of lymphoid and splenic tissue are associated with a loss of natural (3) and acquired resistance (4) to grafting with tumor tissue. However, attempts to furnish direct experimental proof for the existence of an activity of R.E.S. or splenic tissue antagonistic to neoplastic cells have yielded highly controversial results (1).

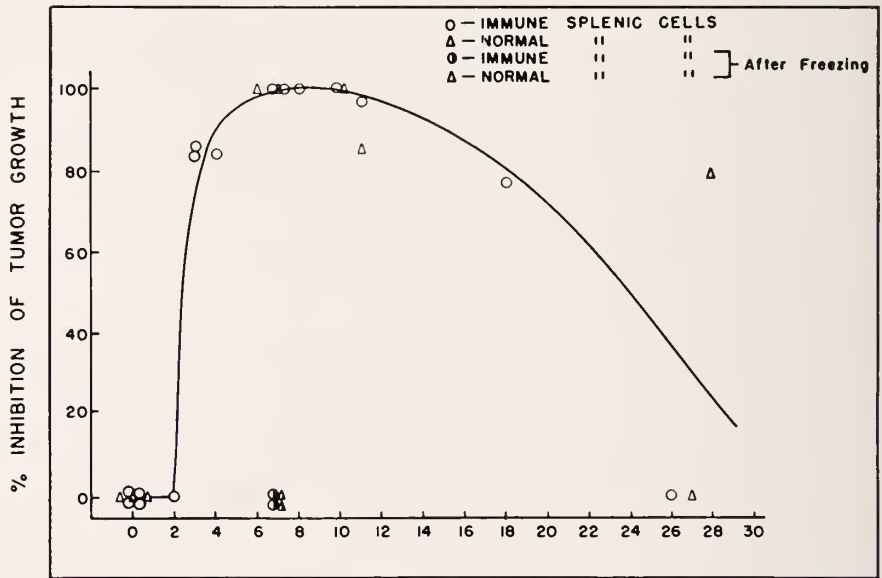
In the following, evidence is presented to show that under certain conditions, injections of homologous lymphoid cells are followed by a delayed development of resistance to grafting with neoplastic cells.

The rats employed in the present study were of the Sprague-Dawley strain (Holtzmann). The tumor grafted was the Murphy rat lymphosarcoma which in these animals takes in all instances and kills 70–80% of the rats in 3–4 weeks. In the remaining animals spontaneous regressions occur 2–3 weeks after the inoculation. Rats in which lymphosarcoma implants have regressed or those in which regressions were induced (4) became resistant to reinoculation with the same neoplasm. For the inoculations, suspensions of lymphosarcoma cells in Gey's solution were prepared under sterile precautions, the cells counted and dilutions containing 250,000 cells per 0.25 cc. injected subcutaneously into groups of rats. The tumors resulting from this injection grew at a sufficiently reproducible rate and after 2 weeks averaged somewhat more than 25 cm³. in size. Cell suspensions from spleen or thymus (20%) were prepared in the same fashion as the suspensions of tumor cells. From repeated counts it was seen that the number of cells in such suspensions, after filtration through sterile glass wool, approximated for spleen 100 million for thymus 300 million per cm³. Unless stated differently, pools of lymphoid organs from several rats were used.

Previously it was observed that suspensions of lymphoid cells of mice or rats in which tumor transplants had regressed, and which subsequently had become resistant to reinoculation with tumor tissue, were cytotoxic to the respective neoplastic cells (5, 6); lymphoid cells from normal animals showed no such activity. However, when attempts were made to passively transfer tumor immunity, it was found that injections of intact lymphoid cells to susceptible rats caused resistance to grafting with lymphosarcoma cells irrespective of whether the lymphoid cells were derived from tumor-immune or from normal rats. This is illustrated by the data summarized in Fig. 1, showing that the intravenous or intraperitoneal (Table 1) injection of splenic or of thymic cells was followed,

* From the Merck Institute for Therapeutic Research Rahway, N. J.

after a delay of 2 days, by resistance to the injection of 250,000 lymphosarcoma cells for a period of up to 26 days. This resistance was limited and was relative to the number of cells in the inoculum. Rats comparable to those which proved resistant to inoculation with 250,000 cells exhibited no measurable loss of susceptibility when they were challenged with 10 million tumor cells. The experiments in Fig. 1 and Table 1 (Exp. A) show that resistance to tumor grafts developed only when uninjured cells were injected, and that lymphoid cells of



DAYS BETWEEN INJECTION WITH SPLENIC CELLS AND INOCULATION

FIG. 1. Twenty-five groups (6 Sprague-Dawley male rats per group) were injected intravenously or intraperitoneally with 1 ccm. of a suspension of splenic cells. Subsequently, at the time intervals indicated on the ordinate, the same 25 groups and 25 control groups were injected subcutaneously with 250,000 lymphosarcoma cells. At the 14th day after inoculation the average size of the tumor transplant was compared in the various groups. The differences in tumor volume between the various experimental groups and their controls are expressed per cent inhibition of tumor growth and are plotted against the number of days elapsed between the injection with splenic cells and the injection with the challenging inoculum.

animals of other species (Table 1, Exp. C) are ineffective in this respect. Suspensions of uninjured cells can be prepared from testes in a similar fashion. The injection of such cell suspensions did not alter the susceptibility of the animals (Table 1, Exp. B). In accordance with previous findings it was seen (Table 2) that cell suspensions or extracts from lymphoid tissue when mixed with tumor cells and then injected into susceptible animals did not retard the growth of the tumors.

Tentative explanations for these observations include the possibility that the resistance acquired by the rats represents an immune response to an antigenic moiety common to both the lymphosarcoma and its prototype cell. If such were the case, the antigenicity of cells of animals within the same species and strain

may have been due to artificial denaturation of cellular proteins during the experimental procedures or may represent a lack of true homology due to iso-

TABLE 1

Depression of tumor growth following injection with homologous lymphoid cells

EXPERIMENT	CELL SUSPENSION INJECTED	INOCULATED WITH LV. SA. AFTER	CCM. TUMOR SIZE 14 DAYS AFTER INOCULATION	NO. OF TAKES
A	Spleen (i.p.)	7 days	3.8 (0-18.1)	5/11
	Spleen (after freezing)	7 days	30.5 (4.5-54.7)	6/6
	—	7 days	23.5 (4.7-35.5)	11/11
B	Testis (i.p.)	7 days	28.6 (0-55.3)	14/15
	—	7 days	22.6 (2.0-36.8)	8/8
C	Rat thymus (i.p.)	7 days	0	0/5
	Chick thymus (i.p.)	7 days	45.3 (12.7-84.7)	4/4
	Guinea pig thymus (i.p.)	7 days	34.7 (21.1-66.4)	5/5
	Rabbit thymus (i.p.)	7 days	29.8 (16.0-53.0)	4/4
	Dog thymus (i.p.)	7 days	33.4 (5.7-52.2)	5/5
	—	—	31.6 (2.0-59.7)	8/8
D	Homologous thymus	7 days	7.9 (0-40.6)	2/7
	Autologous thymus	7 days	35.4 (21.0-63.7)	8/8
	—	—	39.6 (18.1-53.0)	8/8

TABLE 2

Failure of suspensions or extracts of lymphoid cells incubated with tumor cells to alter the viability of the latter

30 MIN. 37° MATERIAL	CCM 14TH DAY	NO. OF TAKES
Spleen	25.5 (13.2-38.1)	6/6
Lymph node	26.1 (16.9-36.6)	5/5
Control	16.2 (4.7-31.5)	5/5
Spleen	30.1 (0-67.8)	6/7
Spleen extract*	24.1 (2.4-33.4)	8/8
Thymus	42.7 (15.1-62.4)	8/8
Thymus extract*	26.7 (15.5-52.5)	8/8
Spleen	27.8 (15.0-43.2)	6/6
Spleen extract*	31.4 (6.8-51.5)	6/6
Control	26.1 (14.1-52.5)	6/6
Thymus extract†	21.9 (2.4-33.4)	6/6
Control	30.9 (10.6-53.0)	6/6

* Freezing and thawing.

† Silica ground.

antigens. From Table 1 (Exp. D) it is seen that partially thymectomized rats injected with suspensions of their own thymic cells failed to develop resistance, while aliquots of the same suspensions injected into other rats greatly diminished

their ability to take tumor grafts. Therefore, the possibility appears eliminated that the injected cells have artificially been rendered antigenic. Although other possibilities cannot be excluded, it appears likely that some form of immunity involving iso-antibodies is responsible for the above findings. Sera and suspensions of lymphoid cells of animals injected with homologous lymphoid cells were

TABLE 3
Incidence of resistance in groups of rats injected with lymphoid cells from single rats

SUSPENSION OF LYMPHOID CELLS FROM SINGLE RATS	INOCULATION WITH LY. SA. AFTER	CCM. TUMOR VOLUME AT 14TH DAY	NO. OF TAKES
1	7 days	0	0/3
2	7 days	1.9 (0-8.8)	2/5
3	7 days	0	0/5
4	7 days	0.3 (0-1.5)	1/5
5	7 days	6.6 (0-18.1)	3/5
6	7 days	6.9 (0-32.5)	2/5
7	7 days	22.3 (0-39.6)	4/5
8	7 days	1.3 (0-6.6)	1/5
9	7 days	9.2 (0-33.4)	2/5
10	7 days	16.6 (0-48.5)	2/3
11	7 days	0	0/5
12	7 days	0	0/5
13	7 days	4.9 (0-19.8)	2/5
Non injected controls		25.5 (6.0-42.2)	10/10

TABLE 4
Suppression of resistance to grafting by cortisone

CELL SUSPENSION INJECTED	TREATMENT AFTER INJECTION	INOCULATION WITH LY. SA. AFTER	TUMOR SIZE AT 14TH DAY	NO. OF TAKES
Spleen (i.v.)	—	7 days	3.5 (0-18.1)	3/9
Spleen (i.v.)	Cortisone 5 mg. for 18 days*	7 days	22.6 (0-57.2)	7/10
—	Cortisone 5 mg. for 18 days*		32.7 (14.7-52.2)	10/10
Thymus (i.v.)	—	7 days	13.5 (0-63.7)	3/10
Thymus (i.v.)	Cortisone 5 mg. for 13 days*	7 days	3.0 (1.0-8.4)	9/9
—	Cortisone 5 mg. for 13 days*		7.9 (1.5-16.9)	9/9
—	—		58.6 (31.6-93.0)	9/9

* The cortisone injections were started immediately after the intravenous injection of lymphoid cells.

examined for activity cytotoxic to lymphosarcoma cells but were found inactive. Also, washed rat erythrocytes were not agglutinated by such sera. These negative findings, especially in view of the fact that the supposed antigen was injected only once, are obviously inconclusive. If factors like those involved in blood groups are suspected to play a role, it may at first seem difficult to understand the high incidence of success with which an unselected rat population is rendered resistant when injected with lymphoid cells from single rats (Table 3).

However, this is perhaps no more surprising than the absolute incompatibility of homo-transplants of skin or other organs among all animals of the same strain except for those of monozygotic origin.

Previously it was suggested that cortisone inhibits the formation of immune body (7) as well as it suppresses the unclarified immunity involved in the tuberculin type of hypersensitivity (9) or "tumor immunity" (4, 6). From the experiments summarized in Table 4 it can be seen that the acquired resistance to grafting with lymphosarcoma cells is greatly diminished when, following the injection of homologous lymphoid tissue, cortisone is administered prior to the challenging inoculation. Recently it was observed that the administration of cortisone prolongs the persistence of homologous transplants of skin (9) and of kidney (10) as well as it counteracts the ill effects of incompatible transfusions. Furthermore, diseases like certain hemolytic anemias (11) and thrombocytopenic purpuras (12) were found to be benefited by cortisone. In all these instances some type of immunity of undefined nature is assumed to play a role. There is little reason to believe that the present findings bear on the problem of spontaneous neoplastic disease. It is likely that they concern a poorly understood immunity related to certain iso-antigens. It is possible that the controversial results concerning the activity of splenic and R.E.S. tissue upon transplanted neoplasm can be explained on the basis of the present findings.

SUMMARY

Rats injected with intact, homologous lymphoid cells after a delay of two days developed a temporary resistance to grafting with lymphosarcoma cells. The resistance was limited and was relative to the size of the challenging inoculum. The development of the resistance was prevented by the administration of cortisone.

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THE MODE OF ACTION OF ANTIBIOTICS: PENICILLIN AND STREPTOMYCIN¹⁻²

W. W. UMBREIT AND E. L. OGINSKY

[Rahway, N. J.]

Because Dr. Pick has long been active in the study of the mode of action of drugs we are happy to present this summary on the mode of action of antibiotics.

Any discussion of this topic is somewhat limited for two reasons; first, the term "mode of action" means different things to different people. Second, the "mode of action" in the biochemical sense is not well known for most antibiotics. We shall therefore confine our attention to the two older ones with widespread, effective, clinical use, that is to penicillin and to streptomycin. At some later date, when more information is available on the biochemical mode of action of other antibiotics, a more general treatment may be in order. With these limitations, there are to our minds three important aspects of the problem of "mode of action" of these antibiotics. This approach is based on the philosophy of Immanuel Kant, that Reason should approach Nature, not in the character of a pupil who listens to all that his master chooses to tell him, but rather, in the character of a judge who compels the witness to reply to those questions he thinks fit to propose. We consider that the following three questions are pertinent to the mode of action of antibiotics and shall outline the information relating to each question first for penicillin and then for streptomycin. The questions are the following:

First, what are the vulnerable points in the biochemistry of the cell that the antibiotic attacks?

Second, what is the basis of the specificity of the antibiotics: That is, why can they be used *in vivo*?

Third, what happens to the vulnerable points in metabolism when resistance to the antibiotic develops? This is not a question of the genetic mechanism whereby resistance can develop, but rather the altered metabolism of the cell after resistance has developed.

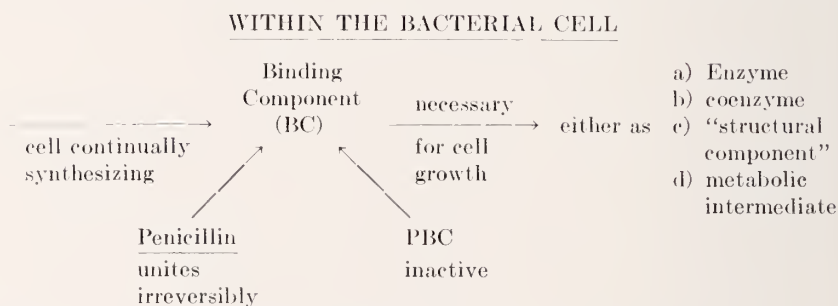
Since the literature on both penicillin and streptomycin is so voluminous, we shall restrict our attention to these three questions and ignore a variety of related information which does not bear directly upon them.

It is to be understood in the following discussion that the effects described are specific for the antibiotically active forms of the drug and are uninfluenced by chemical modifications or degradation products which have lost antibiotic activity. And further, that the reactions described are sensitive to the antibiotic in concentrations of the same order of magnitude as those required to inhibit growth *in vitro* or to provide clinical efficacy.

¹ From the Merck Institute for Therapeutic Research, Rahway, N. J.

² Presented at the Antibiotics Symposium of the Medicinal Chemistry Division Diamond Jubilee Meeting of the American Chemical Society, New York, N. Y., on September 4, 1951.

We shall first consider the mode of action of penicillin. Obviously, before a drug can react it must be adsorbed by the organism and be in physical contact with sensitive loci. After some confusion, such an adsorption is now well established, due to the work of Rowley and associates (1) and of Maass and Johnson (2, 3). The latter workers found a specific adsorption of penicillin independent of the extracellular penicillin concentration comprising close to 750 molecules of penicillin per cell as well as a diffusion of penicillin into the cells over and above this point. This specifically absorbed penicillin was not exchangeable and remained bound during subsequent growth of the cells in a penicillin free medium. The interpretation (fig. 1) placed upon the data is that during growth the cell synthesizes the penicillin "binding component" (BC). The synthesis of this component is not inhibited by penicillin, but the penicillin unites with it once it has been formed, thus preventing either its activity (if one supposes it to be



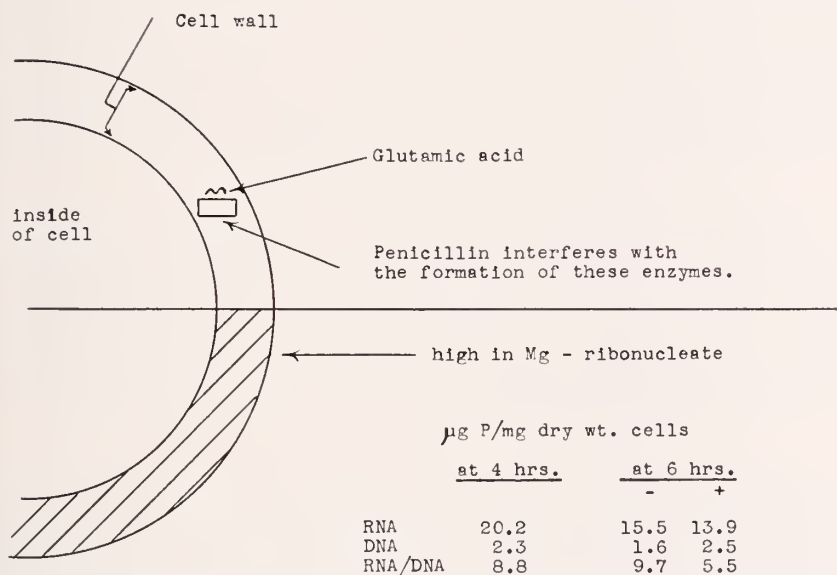
Based on data of Maass and Johnson, *J. Bact.* 57, 415 (1949). 261 (1949).

FIG. 1

an enzyme or coenzyme) or its further metabolism or utilization. The lowest bacteriostatic penicillin concentration is that at which the union with the specific penicillin binding component is slightly more rapid than its resynthesis by the cell. Since the rate of synthesis of "binding component" (BC) may vary with the species of organism, one would not expect too close a correlation between the sensitivity to penicillin and the amount of specifically bound penicillin, but in general a fair correlation is found (3).

The next problem is the nature of "binding component." This is not known, but several observations give one a hint as to the type of reaction with which "binding component" is concerned. The location of this material is most probably at or near the cell surface, but wherever it may be, one may determine a variety of effects due to its lack of function in the presence of penicillin. We propose merely to briefly summarize the present situation as we see it. Neglecting a variety of excellent experimental work, which in our opinion constitutes further examples of the phenomena described, we shall concentrate upon three examples of investigations showing what happens to cell metabolism when penicillin unites with "binding component." The first of these are the studies of Gale (4) which are paraphrased with the following picture (figure 2). In many

gram positive bacteria, glutamic acid (and certain other amino acids) enter the cell, not by a simple process of diffusion, but by an active process, enzymatically catalyzed, which requires energy. The amount of glutamate which enters is controlled by the amount of energy available. Penicillin does not interfere with the metabolism of glutamate once it is inside the cell nor does it interfere with the catalyzed passage of glutamate into the cell once the enzymes concerned with this process (whatever they may be) are formed. But penicillin does interfere with the formation of these glutamic transporting enzymes. Penicillin, of course, acts primarily upon gram-positive bacteria. In these organisms, the outer layer, responsible for their gram-positive character is rich in magnesium



Gale, Bull. Johns Hopkins Hospital 83, 169-175 (1948).

FIG. 2

ribonucleate. Penicillin inhibits the synthesis of ribose nucleic acid, as may be seen from the data in the lower portion of Figure 2, particularly that relating to the RNA/DNA ratios. First, then, one of the effects of penicillin or rather of the inactivation of the "binding component" is to prevent the formation of the enzymes concerned with glutamate transport and to inhibit RNA synthesis relative to DNA synthesis. In this case one is measuring the lack of end products, e.g. the glutamic transport system, when the reaction sensitive to penicillin is inhibited. The lack of function of the binding component may be manifested in other ways since some gram positive bacteria are apparently not dependent upon this particular type of glutamic transport (5).

Park and Johnson (6) used a different approach and discovered some intermediates which accumulate when penicillin is present (fig. 3 -recalculated from Park and Johnson (6)). As the cells grow in the absence of penicillin the total

phosphorus per cell and the labile (Δ_7) phosphorus per cell tend to remain constant. But in the presence of penicillin, although growth is inhibited, phosphorus uptake continues, so that the phosphorus content per cell increases and particularly the labile phosphorus content per cell increases markedly. Later unpublished work of Dr. Park has shown that the labile phosphorus exists in the form of at least three uracil-pentose-complexes one of which has also been isolated from normal cells. These materials are apparently intermediates whose further metabolism is prevented by penicillin. That is, these are either the substrates of the penicillin inhibited enzymes or products of these substrates by side reactions. It takes no great stretch of imagination to see the relationship between these intermediates and the uridine-5-phosphate or the uridine-phospho-glucose of whose functions, through the work of Leloir and associates (7, 8) we are only beginning to be aware.

As a third example, we would cite the work of Hotchkiss (9), who has shown that while penicillin in resting cells does not inhibit the uptake of various amino acids, it does inhibit their conversion into cellular protein. Instead, in the pres-

PARK AND JOHNSON, J. Biol. Chem. 179, 585 (1949)

GROWING CELLS	CELLS AT ZERO TIME	65 MIN. LATER	65 MIN. LATER + PENICILLIN
Total P	14.2	13.9	22.4
Labile P	1.8	1.9	5.6

P calculated as $\mu\text{g P per } 10^{10} \text{ cells}$.

FIG. 3

ence of penicillin, resting (non-growing) cells form a non-amino nitrogenous material which gives a biuret reaction and has properties suggestive of a peptide. The material has, to our knowledge, not been further identified. This is, of course, another example of a substance which accumulates when the penicillin sensitive component is inactivated. Other examples of similar types of phenomena could be cited, such as the studies by Simmonds and Fruton (10), etc. In brief, all of these are observed phenomena; are alterations in metabolism, either the accumulation of intermediates or lack of formation of end products, when the penicillin binding component is irreversibly inactivated by penicillin.

The second question, "why is penicillin able to enter the animal, kill off the susceptible bacteria therein without harm to the host?"—is not answerable experimentally by any data known to us. Perhaps the "binding component" does not exist in the animal cell, perhaps the reactions catalyzed by the "binding component" are not important in animal cell metabolism and doubtless there are other possibilities. Since we know of no studies devoted to this problem, one can only point out that there appears to be a difference in the metabolism of gram-positive and gram-negative or animal cells which makes this specificity of penicillin possible.

The third question is the alteration of metabolism when resistance develops. For purposes of clarification we have summarized in Figure 4 the possibilities

available to an organism in the development of resistance to drugs in general. With respect to resistance to penicillin, several of these have been noted. First, there are certain organisms, such as most of the yeasts, which are resistant to penicillin because of the inability of penicillin to penetrate into the cell. However, the vast majority of organisms are resistant to penicillin because of the second alternative, i.e. they possess or develop an enzyme, penicillinase, which destroys the drug. But finally, some organisms exist (and this is the group we are concerned with) into which penicillin penetrates and which possess no penicillinase, yet they are still resistant. Studies on the amount of "binding component" show no consistent results; "binding component" may be present or absent, and its occurrence and amount appear to be purely a matter of chance. To our knowledge, there have been no studies on the accumulation of intermediates in resistant cells, such as those of Park and Johnson or Hotchkiss on sensitive cells. But the approach on end products, principally following the work of Gale, has been fruitfully studied. It is possible to make a generalization

POSSIBILITIES FOR RESISTANCE

A sensitive organism can grow in the presence of a toxic drug if it makes one or more of the following changes:

1. Becomes impermeable to the drug.
2. Develops a reaction destroying drug.
3. Alters its metabolism so that:
 - a) with a competitive drug, it makes more substrate.
 - b) employs another path to the product(s) of the inhibited reaction.
4. Alters the sensitive enzyme(s) so that it is no longer sensitive.

FIG. 4

that the most probable mechanism of resistance is #3, b, the development of an alternative pathway to the products of the inhibited reaction. We base this conclusion on the studies of Bellamy and Klimek (11), and Gale and Rodwell (12), who found that as gram-positive cells became resistant they tended to become gram-negative and to exchange the energy requiring mechanism of glutamate transport for one of simple diffusion or one of internal synthesis thus by-passing the transport mechanism whose formation was inhibited by penicillin.

It should be emphasized that the changes in metabolism associated with the development of resistance to drugs may be neither singular nor necessarily specific. If we consider that an organism must dispense with the sensitive reaction series, it must then develop another series to accomplish the same end. This so-called "by-pass" may put additional strain on the organism and it may be necessary to make several other metabolic alterations to accommodate the new pathway. These alterations may engender further requirements, for example, the requirement for more of a given amino acid or vitamin than was previously needed. Thus various deficiencies in growth requirements may or may not appear, depending upon the "by-pass" it is necessary to employ and upon the genetic and environmental capacities of the cell. In addition, reactions leading into the older pathway, now by-passed, may be lost through disuse, or may be

diverted into other channels, or, indeed, the organism may use both pathways depending upon whether or not the toxic agent is present. Because of these possibilities one may, indeed one does, find a variety of alterations in resistant cells, some, closely related to the by-pass mechanism itself, and some, secondary changes arising from the considerations just described. An experimental problem of some importance is to distinguish between the primary and secondary changes, and admittedly because of certain difficulties in working with penicillin, this has not yet been done with certainty.

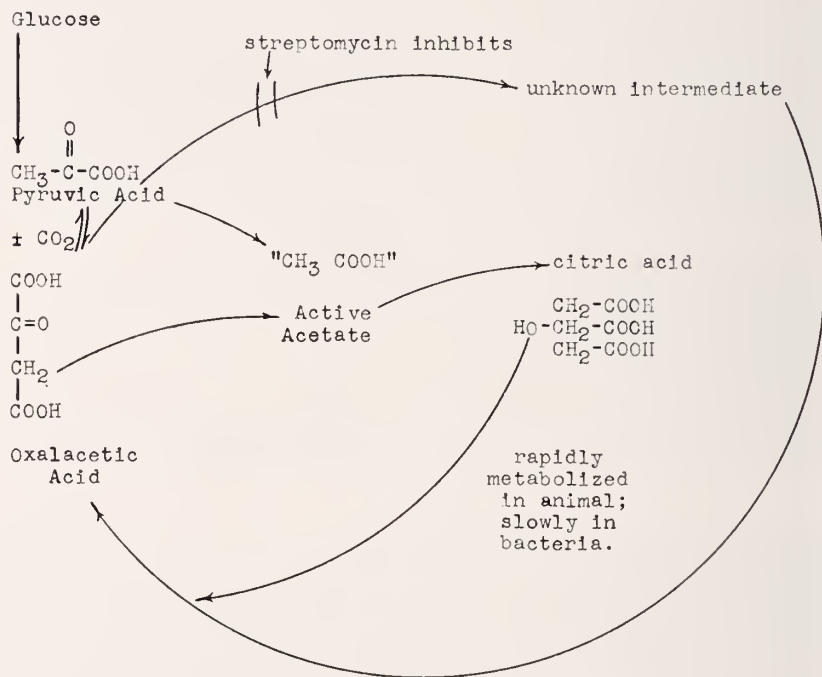


FIG. 5

Early studies on the mode of action of streptomycin were confused by the fact that streptomycin inhibits the formation of adaptive enzymes. Only later did evidence accumulate that it shares this property with a wide variety of antibiotics, such as aureomycin and chloromycetin, indicating that the inhibition is non-specific in character. Further, adaptive enzymes can frequently be formed in non-multiplying cells. Hence some of the earlier work is in reality a reflection of this phenomenon, rather than evidence of a specific type of streptomycin inhibition. But to return to the questions we have seen fit to propose to Nature, a specific vulnerable point in the biochemistry of the cell which has been found susceptible to streptomycin is the oxalacetate-pyruvate-reaction (fig. 5). Streptomycin thus inhibits the entrance of various compounds into the terminal respiration system of the susceptible organism. Five types of evidence are available from which these conclusions were drawn (data summarized (13)).

First, the stimulation of amino acid oxidation by previous organic acid oxidation as described by Geiger (14) was traced to the formation of an intermediate, probably oxalacetate, which reacted with the keto acid derived from the amino acid (15). The conversion of serine to pyruvate and threonine to α -keto butyrate and the condensation of these with oxalacetate was the cause of the Geiger phenomenon. This condensation was inhibited by streptomycin (15).

Second, cells of *E. coli* containing an active oxalacetate decarboxylase and thus able to equilibrate rapidly oxalacetate and pyruvate, show a markedly inhibitory effect of streptomycin on oxygen uptake when oxalacetate is present (in these circumstances actually a mixture of pyruvate and oxalacetate), although streptomycin is essentially without effect when pyruvate alone is present (16). The effect of streptomycin may be obtained either by oxalacetate addition in the absence of bicarbonate or by pyruvate addition in the presence of bicarbonate and under either aerobic or anaerobic conditions. The recent note by Barkulis (17) which appears to involve pyruvate directly, actually involves pyruvate and bicarbonate and thus oxalacetate under the conditions employed.

Third, cells of *E. coli* may be treated to remove the oxalacetate decarboxylase, so that pyruvate and oxalacetate are not in equilibrium (16). Such cell preparations oxidize pyruvate to the stage of acetate, uninfluenced by streptomycin. They oxidize oxalacetate very slowly, and the oxidation that does occur probably follows its spontaneous decarboxylation to pyruvate. But these cells oxidize a mixture of oxalacetate and pyruvate very rapidly. In the absence of streptomycin this oxidation tends to proceed toward complete oxidation; in the presence of streptomycin oxidation is inhibited and stops at the oxidation state of acetate.

Fourth, preparations can sometimes be made (15), unfortunately not with much certainty, which do not oxidize either pyruvate or oxalacetate, but will rapidly oxidize a mixture of the two. The oxidation of the mixture is completely inhibited by streptomycin. Fifth, all of these observations may be fitted into, and in fact serve as the basis for, the hypothesis shown in Figure 5, i.e., that pyruvate plus oxalacetate condense to form unknown intermediates which are oxidized by a cyclic process resembling the citric acid cycle and that streptomycin inhibits this condensation. If this were the case, then in the presence of streptomycin, succinate, malate, fumarate, etc., should be oxidized to the oxidation state of acetate while in the absence of streptomycin they should go around the cycle and be oxidized toward completion. This is indeed the case (16).

On the surface this terminal oxidation system would appear to be a typical citric acid cycle. In this case, citrate should be the intermediate. Unfortunately it is not (18). Streptomycin does not inhibit the acetate-oxalacetate system of Stern and Ochoa (19). Further, streptomycin does not interfere with the formation of citrate by the intact bacterial cell and it appears that citrate is not an intermediate in the oxidative cycle with which we are concerned (18). While streptomycin exhibits a marked inhibitory effect on the oxidation of oxalacetate and pyruvate, it actually increases citrate formation slightly. The citrate is formed early and then remains at a relatively constant level even though sub-

strate has been exhausted. At the moment we do not know the mechanism of the oxalacetate-pyruvate reaction inhibited by streptomycin, but the reaction can be measured quite readily.

It is evident, of course, that this type of reaction, i.e. entrance into the terminal respiration system, is an important part of animal metabolism. Why, then, can streptomycin be put into the animal without harm, or at least comparable harm, to the host? Without going into detail, the evidence shows (20) that a permeability barrier to streptomycin exists at the cell wall and at the surface of the mitochondria. The reaction we are dealing with is located within the mitochondria. Streptomycin is an antibiotic because it does not penetrate to sites of the sensitive reaction in the animal cell. If it is put there artificially, however, it is a very powerful inhibitor of the animal enzyme. Evidence for the cell wall as a permeability barrier against streptomycin has also been obtained by other types of investigations. For example, Magoffin and Spink (21) found that phagocytized brucella were largely unaffected by doses of streptomycin lethal to extracellular brucella.

Our third question is what happens metabolically when resistance develops? Evidence shows that the oxalacetate-pyruvate reaction is lost (22). In the case of the resistant strains described in published data (22), the oxidation of pyruvate and oxalacetate even to the stage of acetate is extremely low and the oxidations of succinate, fumarate, malate, etc., were also similarly affected. In a variety of other strains studied, it was found that the loss of the pyruvate to acetate reaction, or the loss of ability to oxidize the dicarboxy acids was largely a matter of chance since some strains retained these abilities; but consistently, whenever a resistant strain was obtained, the oxalacetate-pyruvate reaction was missing. It is curious that in resistant strains, even though oxidation of oxalacetate and pyruvate is lost, the ability to form citrate from these compounds is present, and indeed enhanced (18). Similarly in the strains dependent upon streptomycin for growth, the oxalacetate-pyruvate reaction is missing (22). The data are sufficient to conclude that whenever one obtains growth in the presence of streptomycin, the oxalacetate-pyruvate reaction is not present in the cells.

There have been several other proposals for a site of action of streptomycin and indeed streptomycin does act as a precipitant of nucleic acids (23), inhibits diamine oxidase (24) and various other actions have been reported (25, 26). In all of these cases, however, the two criteria which are employed to specify the antibiotically important reaction have not been met. These criteria are that the effect described must be specific for the antibiotically active form of the antibiotic and are affected by the antibiotic in concentrations comparable to those required to inhibit growth. Until these criteria have been satisfied, the relationship of the various effects of streptomycin reported to its mode of action in inhibiting the bacteria remains obscure.

With this information there are certain generalizations which may now be drawn. Penicillin and streptomycin have in common the following aspects of their mode of action. The implication, of course, is that these aspects are characteristic of antibiotics in general, but this we do not know.

1. They combine with a specific enzyme system (not the same one) in an irreversible manner.

2. Whenever resistance develops the reaction sensitive to the drug is lost from the resistant cell and thus is presumably by-passed.

Penicillin and streptomycin differ in the following aspects of their mode of action:

1. In the nature of the reaction inhibited.

2. In the reasons why they can be used in the animal, that is, in the fundamental basis for their specificity.

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EINFLUSS DES DESOXYCORTICOSTERONS UND ANDERER STERINE AUF DIE ZELLMEMBRANDURCHLÄSSIGKEIT DER GELENKKAPSEL

P. STERN*

Das Problem der Permeabilität der Zellmembranen ist von grundlegender Bedeutung für das Verständnis der Abwicklung physiologischer und pathophysiologischer Prozesse. Eppingers Theorie (1) der "serösen Entzündung" ist der Versuch einer universalen Deutung der Pathologie gerade aufgrund der gestörten Zellpermeabilität der Organe und Kapillaren. Das neueste Referat Wilbrants (2) weist deutlich auf die immer grösser werdende Wichtigkeit des Studiums der Permeabilität für die Biologie im allgemeinen hin.

Wir (3) haben in unseren Arbeiten häufig das Problem der Permeabilität bearbeitet und sind zu gewissen praktischen Ergebnissen gekommen, z.B. bei der Therapie der Myasthenia gravis. Wir hatten Gründe, anzunehmen, dass es sich bei dieser Krankheit um eine erhöhte Permeabilität der Muskelzellmembran und demzufolge um eine Verringerung der Intensität der Reizübertragung handele. Demnach müsste die Herabsetzung der Permeabilität der Muskelzelle zur Besserung des Krankheitszustandes führen. Wir erreichten die Herabsetzung der Permeabilität, indem wir eine allergische Reaktion hervorriefen, welche nach Heim die Permeabilität herabsetzt und den Tonus des cholinergischen Systems erhöht. Wir konnten die Herabsetzung der Permeabilität infolge Bindung von Antigenen mit Antikörpern auf der Zelloberfläche auch experimentell beweisen (5). Tatsächlich kam es bei unsern Patienten zur augenblicklichen Besserung des klinischen Bildes nach der Reinjektion des homologen Antigens. Da sich die allergische Reaktion beim Menschen nicht wiederholen lässt, versuchten wir mit anderen Mitteln die Permeabilität der Muskelzellmembranen bei den Myasthenikern herabzusetzen und zwar mit Hilfe der Sterine. Wir verabreichten intravenös Decholin. Der Effekt war viel besser als nach einer allergischen Reaktion und dauerte viel länger. Der Grund, weswegen wir Decholin verwendeten, war der, dass es den Anschein hat, als ob die Sterine ohne Rücksicht auf spezifische Unterschiede sämtlich die gemeinsame Fähigkeit besitzen, die Permeabilität herabzusetzen.

Bereits bei der Myasthenia gravis wurde ausser Decholin mit Erfolg auch AT-10 (6) und Cortin (7) versucht. Andererseits ist bekannt, dass auch die Wirksamkeit der herzaktiven Glykoside mit deren Wirkung auf die Membran erklärt wird (8). Auf den Herzmuskel wirken viele Sterine in gleicher Weise wie Digitalis. So können z.B. Gallensäuren (9), Vitamin-D (10), männliche Geschlechtshormone (11) herzaktive Glykoside ersetzen. Auch bezüglich des Kohlehydratwechsels im Herzmuskel verhalten sich die verschiedenen Sterine gleichartig (12). Unser Versuch an der Beri-beri-Taube zeigte, dass Digitoxin die Permeabilität in gleicher Weise herabsetzt wie eine allergische Reaktion (8d).

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Sogar auch Saponin Digitonin, welches Sterin-Struktur besitzt, vermindert die Permeabilität der Zellmembran des Myokards (13), obschon es bei Erythrocyten Hämolyse hervorruft.

Weese's Einwand (14), dass ein herzaktives Glykosid in therapeutischen Dosen lediglich drei von Hundert der Oberfläche der myokardialen Zellmembranen bedecken könnte u.zw. mit einem monomolekularen Film, bleibt nicht unwidersprochen. Danielli und Davson (15) machen darauf aufmerksam, dass verschiedene Molekeln bei verschiedenen Poren eindringen, und es deswegen nicht notwendig sei, dass die Oberfläche einer Zelle für das Eindringen einer Materie vollständig bedeckt werde. Bei der Wirksamkeit der herzaktiven Glykoside wäre dies der Fall des Acetylcholins. Ausserdem bleibt die alte pharmakologische Frage offen, ob auf der Zelloberfläche tatsächlich Glykosid abgelagert wird oder ob funktionelle Veränderungen auf der Membran zurückbleiben.

Alle diese Angaben werden deswegen vorangestellt, um auf die Verwandtschaft der einzelnen Sterine untereinander und auf die Möglichkeit des Austauschs des einen durch das andere hinzuweisen, sowie auch, um ihre gemeinsame, zellabdichtende Wirksamkeit hervorzuheben. Nämlich demselben Problem in der gleichen Form werden wir bei der Deutung der Wirksamkeit des Cortisons bei akutem Rheumatismus begegnen. Der akute Rheumatismus ist nach Eppinger eine allgemeine Erkrankung der Kapillaren im Sinne einer akuten Glomerulonephritis. Witzgal (16) hat darauf aufmerksam gemacht, dass auch einige andere Sterine ausser Cortison antirheumatische Wirksamkeit besitzen. Und noch vor der Ära des Cortisons wusste man das auch vom Vitamin D (17). Wir sehen also, wie ganz verschiedene Sterine sich in der Wirksamkeit bei Rheumatismus ablösen, wie dasselbe auch betont wurde für die Wirksamkeit auf das Herz. Heilmeyer (18) hebt ausdrücklich die zellabdichtende Wirkung des Cortisons hervor und erachtet sie für einen wichtigen Faktor seiner Wirksamkeit auf die Besserung des Krankheitsverlaufes. Demnach müssen wir voraussetzen, dass auch die übrigen angeführten Sterine, die antirheumatisch wirksam sind, zellabdichtend wirken. Diese Wirksamkeit der Sterine wäre eine nichtspezifische.

Eichholtz (19) andererseits weist auf die Tatsache hin, dass auch Desoxycorticosteron, der Antagonist des Cortisons, in grossen Dosen die Durchlässigkeit der Zellmembranen und Kapillaren herabsetzt, und dass es vielleicht deshalb in grossen Dosen antirheumatisch wirkt, was Lewin (20) auch an Patienten erprobt hat. Demnach eröffnet sich die Frage: wie beeinflusst Desoxycorticosteron und die anderen Sterine die Durchlässigkeit der Gelenkmembran. Wir stellen diese Frage gerade im Anschluss an die Tatsache, auf welche Eichholtz aufmerksam macht, dass Doca in grossen Dosen antirheumatisch wirkt. Demnach handelt es sich bei den einzelnen Sterinen und ihrer antirheumatischen Wirksamkeit, konkreter, bei ihrer Wirksamkeit auf die Zellmembran, lediglich um quantitative Unterschiede, nicht jedoch um qualitative. Die Membran der Gelenkkapsel wird ihrer Funktion nach gewöhnlich ähnlich der Membran der Kapillaren aufgefasst, oder wenigstens ähnlicher derjenigen der Membran der Kapillaren als der Membran der Organzellen.

Methode: Wir bedienen uns einer eigenen Methode (5), welche uns gestat-

tete, die isolierte Gelenkmembran unter physiologischen Bedingungen zu untersuchen. Die Methode stammt in der Tat von Winterstein (21), und Heim (22) hat sie modifiziert. Wir haben Heims Methode vervollkommnet und für das Gewebe warmblütiger Tiere umgearbeitet. Der Durchgang der Ringer-Lösung durch den Boden einer lebenden Membran an einem Cylinder kommt in Centimetern zum Ausdruck, gemessen auf einer horizontalen Kapillare oben auf dem genannten Cylinder. In jedem gegebenen Augenblick lässt sich der Cylinder mit Hilfe eines Syphons inhaltlich entleeren und mit einer neuen Flüssigkeit anfüllen. Wir haben den Einfluss auf die Durchlässigkeit der isolierten Zellkapsel der Kälbet (articulatio metacarpophalange) bei Desoxycorticosteronglykosid*, Perlatanglykosid, Decholin, Calciferol und Digitoxin. Die ersten drei sind wasserlöslich, während man dem Digitoxin und dem Calciferol (9%) leichte Konzentration Aethanol zum Zwecke der Löslichkeit hinzufügen muss. Es wurde derartig vorgegangen, dass vor jedem Versuch zuerst Ringer-Lösung in den Cylinder

TABELLE I

Präparat	KONZENTRATION	WIRKUNG
+ Desoxycorticosteron glykosid	10^{-5}	vermindert die Permeabilität
+ Desoxycorticosteron glykosid	10^{-6}	unbestimmt
+ Desoxycorticosteron glykosid	10^{-7}	unbestimmt
+ Desoxycorticosteron glykosid	10^{-8}	erhöht die Permeabilität
Perlatanglukosid	10^{-5}	ohne Wirkung
Perlatanglukosid	10^{-8}	ohne Wirkung
Decholin	10^{-5}	vermindert die Permeabilität
Decholin	10^{-8}	ohne Wirkung
Digitoxin	10^{-5}	vermindert die Permeabilität
Digitoxin	10^{-8}	ohne Wirkung
Calciferol	10^{-5}	vermindert etwas die Permeab.
Calciferol	10^{-8}	ohne Wirkung

kam und fünfminutenweise das Weiterücken an der Kapillare gemessen wurde, u.zw. mindestens viermal. Das dient zur Kontrolle. Danach wird die reine Ringer-Lösung entfernt und die Ringer-Lösung mit der Prüfsubstanz in den Cylinder gegossen. Die Messung ist wieder eine viermalige u.zw. alle fünf Minuten. In der Hauptsache verwandten wir Konzentrationen 1:100,000 und 1:100,000,000. Wir wollen hier nicht jeden Einzelversuch vorführen, sondern lediglich die Endergebnisse von einigen gleichstarken Konzentrationen.

Einige Experimente zeigen Erhöhung, andere Herabsetzung der Permeabilität.

Wie aus den vorgetragenen Ergebnissen ersichtlich, vermindern alle überprüften Sterine ausser Perlatan- in der Konzentrierung von 10^{-5} die Permeabilität der Gelenkkapsel, bleiben jedoch in der tausendfach grösseren Verdünnung von 10^{-8} wirkungslos, ausgenommen das Desoxycorticosteron. Allein Desoxycorticosteron erhöht ausgesprochen die Permeabilität. Also dürfen wir sagen, dass es sich um quantitative nicht aber um qualitative Unterschiede zwischen den ein-

* Das Desoxycorticosteron verdanken wir der Firma CIBA-Basel und das Decholin der Firma Riedel de Haen—Hanover.

selenen Sterinen bezüglich der Permeabilität handelt, und dass allein Desoxycorticosteron in kleinen Konzentrationen, wie sie in den Organismus gelangen, tatsächlich so wirkend wird, dass es die Entstehung einer Entzündung fördert, da es die Permeabilität erhöht. Dieser Befund stimmt vollkommen überein mit der bereits citierten Arbeit von Eichholtz über den Unterschied in der Wirkungsweise kleiner und grosser Dosen Desoxycorticosteron; und Heilmeyer stellen fest, dass Sterine zellabdichtend wirken, wenigstens in grösseren Konzentrationen. Witzgall (16) wie gesagt, hat das schon an Patienten bestätigt und vom Vitamin D (17) wusste man es schon vor dem Cortison, dass es antirheumatisch wirkt. Es ist auch nicht so wesentlich, wie Witzgall hervorhebt, dass die antirheumatischen Sterine in 11 Position die Oxy-Gruppe haben, wie das amerikanische Autoren betonen. Das sehen wir auch schön aus unseren Experimenten. Interessant ist, dass Eppinger Pyramidon verabreichte, gleichfalls in der Absicht, die Permeabilität der Kapillaren herabzusetzen und somit, wie er sagt, die "Albuminurie ins Gewebe" zu verhindern.

An dieser Stelle möchten wir die Wichtigkeit eines Gedankens hervorheben, wie ihn unlängst Weese (14) aufgebracht hat, nämlich dass zu erwarten ist, dass wir bei der physiologischen und pharmakologischen Untersuchung der Sterine auf ein allgemeines biologisches Prinzip stossen werden. Wir haben versucht, die Wichtigkeit dieser Substanzen für die heutige Auffassung der Wirkungsweise der Antirheumatika und der Wirksamkeit der herzaktiven Glykoside hervorzuheben. Deshalb haben wir auch auf die Verwandtschaft der Wirkungsweisen hingewiesen, obschon es sich einmal um die Gelenkkapsel, das andere Mal um die Membran der Myokardzelle handelt.

Von Interesse ist auch, dass Ruzsnyak (23) mit Histamin den Verlauf des akuten Gelenkrheumatismus günstig beeinflussen konnte. Wir erklären das ebenfalls mit der zellabdichtenden Wirkungsweise des Histamins, wie das aus unseren Versuchen an der Beri-beri-Taube (8d) und an der isolierten Meerschweinchenmuskulatur hervorgeht (5). Wir mussten zu einem Schlusse kommen, wo wir mit Eppinger nicht übereinstimmen, nämlich, dass Histamin allerdings die Permeabilität der Kapillarmembran erhöht, jedoch nicht diejenige der Muskelzellmembran, und, nach unseren Messungen, auch nicht diejenige der Gelenkkapsel.

	KONZENTRATION	WIRKUNG
Histamin HCl	10 ⁻⁵	vermindert die Permeabilität
Histamin HCl	10 ⁻⁸	vermindert die Permeabilität

Demnach war die Wirkung, die Ruzsnyak erreichte, im Prinzip die gleiche wie mit den Sterinen. Daher eröffnet sich schliesslich die Frage, ob Antihistaminika und Lokalanaesthetika direkt zellabdichtend (24) oder auch indirekt wegen der Verhinderung der Histaminwirkung, welches die Antihistaminika selbst im Blut des gesunden Menschen vermehren (25). Unsere Versuche mit direkter Messung des Einflusses von Antistin auf die Permeabilität der Membran der Muskelzelle des Meerschweinchens (5) haben gezeigt, dass Antistin die Permeabilität beeinflusst, was zugunsten der aufgestellten Hypothese spricht.

ZUSAMMENFASSUNG

1. Desoxycorticosteronglucosid, Decholin, Digitoxin und Calciferol haben die Eigenschaft, in der Konzentration von 10^{-5} die Durchlässigkeit der Kalbsgelenkkapsel für Ringer *in vitro* zu vermindern. Perlatanglucosid bleibt in dieser Konzentration ohne Effekt. Alle genannten Sterine, den ersten ausgenommen, haben in der Konz. von 10^{-8} keinen Einfluss auf die Durchlässigkeit, der erste jedoch steigert sie. Demnach fördert Desoxycorticosteron die Entzündung in kleinen Konzentrationen und wirkt antagonistisch auf Cortison. In grossen Dosen wirkt es aber synergistisch, wie das auch Eicholz betont hat.

2. Es wurde auf die im allgemeinen einheitliche Wirkung der Sterine auf die Zellmembranpermeabilität aufmerksam gemacht, beim Rheumatismus sowie auch auf die Membran des Myokard, und anderer, besonders der Muskelgewebe.

3. Histamin vermindert ebenfalls die Permeabilität der Gelenkkapsel.

SUMMARY

1. Desoxycorticosteron glucoside, Decolin, Digitoxin and Calciferol in the concentration 10^{-5} have the property of reducing *in vitro* the permeability of calves synovial membrane for Ringer solution. Perlatanglucosid in the same concentration is without effect. All the mentioned Sterines, except the first, have no effect upon permeability in a concentration 10^{-8} , but the first increases it. Therefore Desoxycorticosteron in low concentration enhances inflammation and acts antagonistically to Cortison. In higher dosages, however, it acts synergistically with Cortison, as has been stated by Eicholz.

2. Attention has been drawn to the generally uniform action of sterines upon cell membrane permeability in rheumatic fever both upon that of the myocardium as especially upon muscle tissue.

3. Histamine likewise reduces permeability of the synovial membrane.

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DIE BEDEUTUNG DER EXPERIMENTELLEN PHARMAKOLOGIE FÜR DIE NEUROLOGIE UND PSYCHIATRIE*

OTTOKAR ARNOLD UND HANS HOFF

Wien

Die Wiener pharmakologische Schule hat eine eigene Note, die durch die Arbeiten zweier Männer, H. H. Meyer und E. P. Pick charakterisiert ist. Sie sahen ihre Aufgabe nicht nur darin, die therapeutische Wirkung neuer Pharmaka zu studieren, sie trachteten auch physiologisches und pathologisches Geschehen festzuhalten und zu erklären. Ernst Peter Pick, der Jubilar dieser Festnummer, war immer ein glänzender Experimentator, der an Hand von Tierversuchen seinen Schülern die Details physiologischen und pathologischen Geschehens vor Augen führte. Die pharmakologisch wirksame Substanz wurde unter ihm zu einem Kettenglied in diesem Ablauf; es konnte immer gezeigt werden, in welcher Weise dieses oder jenes Medikament im physiologischen Geschehen eingreifen könnte und das pathologische Geschehen zu beeinflussen vermag.

Es ist gerade diese Betrachtungsweise der Pharmakologie, die einen innigeren Kontakt mit den Kliniken hat. Die experimentelle Pharmakologie der Wiener Schule wurde ein Teil der Forschungstätigkeit des Klinikers. Auf Grund der von Pick und seinen Schülern gewonnenen Tatsachen haben wir versucht, pharmakologische Reaktionen diagnostisch in die Klinik neurologischer Erkrankungen einzuführen. Wir haben aber auch versucht, Mechanismen physiologischer Natur durch die Bestimmung der Einwirkung solcher Pharmaka festzustellen. Namentlich Zusammenhänge des Systems vegetativer Reaktionen standen im Zentrum unseres Interesses.

Wir kamen daher zum Begriff der psychovegetativen Schaltung und verwendeten Schlafmittel verschiedener Gruppen, um diesen Mechanismus zu klären. Zu diesem Zwecke war es aber notwendig, an bestimmten Angriffspunkten solcher Medikamente festzuhalten. Wir dürfen aber diese Angriffspunkte nicht zu scharf abgrenzen. Es ist selbstverständlich, dass grosse Teile des Zentralnervensystems unter der Einwirkung bestimmter pharmakologisch wirksamer Substanzen stehen müssen. Nichts desto weniger glauben wir, dass bestimmte Medikamente relativ selektiv auf bestimmte Kerngruppen des Zentralnervensystems einwirken können. Es ist durchaus möglich, dass im weiteren Verlauf dieser Einwirkung dann grössere Gebiete, die zunächst nicht betroffen wurden, durch das Medikament oder den Wirkstoff beeinflusst werden; im Allgemeinen ist aber doch zumindestens im Anfangstadium eine bestimmte gerichtete pharmakologische Wirkung nachweisbar.

Wir haben nun versucht, Pharmaka zur Erklärung und Reproduktion bestimmter psychiatrischer Symptome zu verwenden. Wir haben auch neue Medikamente in der Therapie von Psychosen und Neurosen erfolgreich angewendet.

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Erinnert sei nur daran, wie katatone Bilder durch Bulbokapnin erzeugt werden können, wie Schlaf- und Narkosemittel in der Therapie der Neurosen als Narkoanalyse angewendet werden.

So erscheint es zweckmässig, diese Bedeutung experimentellen pharmakologischen Arbeitens in dem Gebiet der Psychiatrie an Hand einzelner Beispiele aufzuzeigen, wobei neueste Untersuchungen und eigene Erfahrungen vornehmlich herangezogen werden sollen.

Zwei Pharmaka sind es, die geeignet erscheinen, ein neues Licht in das komplexe Problem des Erlebnisablaufes und seiner formalen Störungen zu bringen, das Dibenamin und das Lysergsäurediäthylamid.

Gelegentlich der Anwendung des Dibenamins (Hydrochlorid des Dibenzyl-Chloraethylamins) als Hemmstoff der Adrenalinreizwirkung bei arteriellen Durchblutungsstörungen und Hochdruck gelangten eigenartige Veränderungen der formalen Seite des Erlebens zur Beobachtung, die in der zusammenfassenden Darstellung von Walther-Büel als Dibenaminpsychose bezeichnet worden sind. Wiewohl die ersten Beobachtungen von amerikanischen Autoren stammen (Hecht, Focht, Abildskov, Burns, Christensen und Rockwell), darf ihre psychopathologische Analyse doch dem Schweizer Autor zugeschrieben werden.

Die einzigartige Wirkung noch mehr als die Frage der therapeutischen Verwendbarkeit war es, die die klinische Prüfung bei uns veranlasst hat. Über den Angriffspunkt des Dibenamins wissen wir, da Adrenalin selbst in keiner Weise angegriffen wird, dass er an der lebenden Zelle gelegen sein muss, die gegenüber der Reizwirkung des Adrenalins unempfindlich wird. Hierbei vermögen andere Substanzen mit adrenalinähnlichem Effekt aber noch zu wirken, woraus gefolgert werden muss, dass die genannte Blockierung adrenalinspezifisch ist, oder aber den adrenalinähnlich wirkenden Stoffen verschiedene Angriffspunkte an der Zelle zukommen, wie dem Adrenalin selbst.

Im Bereiche der Psychiatrie hat diese Substanz nun zwei verschiedene interessante Probleme aufgerollt, einmal eine Wirkungsumkehr bei bestimmten Fällen von Depression, zum zweiten jene spezifische Veränderungen des Erlebnisablaufes, die unter dem Begriff der Dibenaminpsychose zusammengefasst werden können.

Es waren klinische Beobachtungen, die zu zeigen scheinen, dass bei Patienten mit endogenen Depressionen (Melancholie) kleinste Dosen (0, 5 mg pro kg Körpergewicht) einen deutlich stimulierenden Effekt auf die vegetative Reaktionslage im Sinne einer Verschiebung des Gleichgewichtes nach der sympathikotonen Seite ausüben, der jedoch erst jeweils Tage nach der Applikation sichtbar wurde; grosse Dosen dagegen (um 5 mg pro kg Körpergewicht) liessen sowohl den spezifischen Dibenamineffekt auf vegetative Vorgänge im Test als auch eine klinische Wirkung vermissen.

Die im folgenden gebrachten Kurven zeigen das Verhalten des Blutzuckers, Blutdrucks, der Pulszahl und der Leukozytenwerte nach Gabe von 1 mg Adrenalin jeweils vor und nach Anwendung der verschiedenen Dibenamindosen (Tabelle 1 u. 2). Aus diesen—(an verschiedenen Patienten nachgeprüften)—Kurven geht hervor, dass die Dosis von 0, 5 mg/kg Körpergewicht (stark ausgezo-

TABELLE 1

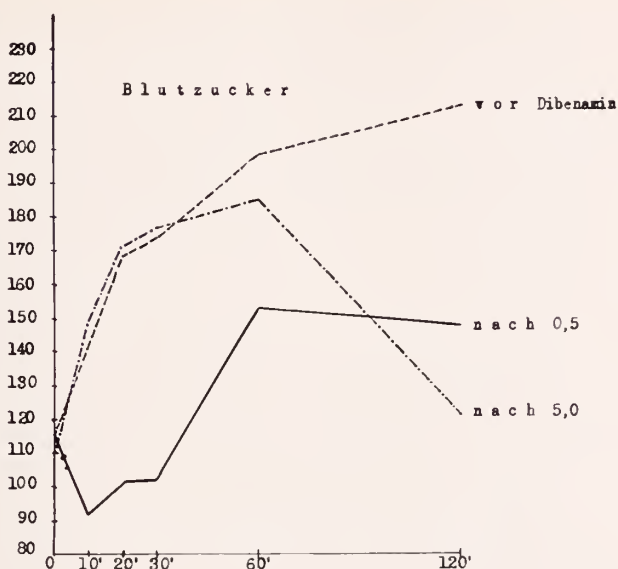
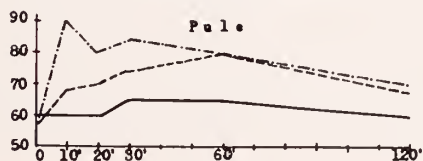
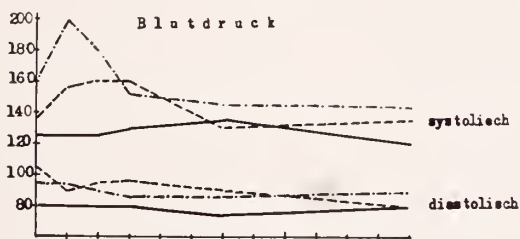
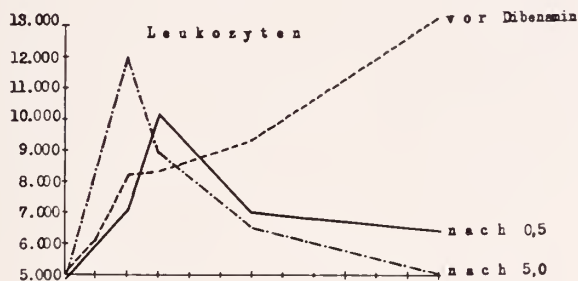


TABELLE 2

Jeweils im Zeitpunkt 0 lag Adrenalin



gene Linie) einen ganz deutlichen adrenalytischen Effekt zeigt, wobei die Kurven 12 Stunden nach Darreichung des Dibenamins gewonnen wurden. 5 Tage nach der Darreichung war der Effekt, wenn auch in geringem Ausmasse, ebenfalls noch nachweisbar. Dagegen zeigte am gleichen Patienten zu einem späteren Zeitpunkt in einer Dosis von 5 mg/kg Körpergewicht zugeführtes Dibenamin (strichpunktierte Linien) den üblicherweise durch Adrenalin auftretenden Reizungseffekt auf Blutbild, Blutzucker, Puls und Blutdruck nicht nur nicht blockiert, sondern in Einzelphasen eher noch verstärkt. Auch dieser Adrenalinversuch wurde 12 Stunden nach Dibenamin durchgeführt und nach 5 Tagen wiederholt, wobei in der Wiederholung ein noch unverändertes Bild gewonnen wurde.

Dem parallel zeigte sich, dass die kleine Dosis von 0,5 mg/kg Körpergewicht etwa am 2. Tag nach der Applikation beginnend, von einer Aufhellung der Depression gefolgt war; in 3 Fällen schien das Medikament sehr wirksam zu sein, während es in 11 anderen Fällen nur eine gewisse Besserung des klinischen Zustandsbildes für mehr oder weniger lange Zeit bewirkte. Einige dieser Fälle waren es, denen nach klinischem Rückfall die grosse Dibenamindosis (5 mg/kg Körpergewicht) gegeben und ihre Wirkung getestet wurde.

Es darf aus diesen Beobachtungsergebnissen vorerst zweierlei geschlossen werden:

1.) Es trifft im Falle der Melancholie das Pharmacon offensichtlich auf eine abnorme Ausgangssituation. Diese wird zum Teil ersichtlich, wenn man die in den Kurven in einfacher Strichlinierung dargestellten Verhältnisse vor Beginn der Dibenamintherapie betrachtet. Schliesslich ist es lange bekannt, dass in der melancholischen Phase eine Verlagerung der vegetativen Normsituation nach der parasympathischen Seite hin erfolgt, wie sich an dem Verhalten von Puls, Blutdruck, Blutzucker usw. ebenso demonstrieren lässt, wie an den klinisch beobachtbaren vegetativen Symptomen der spastischen Obstipation und Sekretionsstörung. Das Beispiel der Melancholie zeigt, in wie starkem Masse der Dibenamineffekt von der vegetativen Reaktionslage abhängig ist, auf die das Pharmacon im speziellen Fall trifft. Wir fanden perorale Zuführung kaum wirksam und alle hier dargestellten Ergebnisse sind ausschliesslich von intravenösen Applikationen gewonnen worden.

2.) Die klinische Wirkung im Sinne eines Stimulans bei entgegengesetzter Wirksamkeit auf die Adrenalinbelastungskurve, wie sie bei der kleinen Dosis auftritt, kann wohl nur als das Wirksamwerden eines gegenregulatorischen Effekts aufgefasst werden. Dieser gegenregulatorische Effekt liess sich in der Folge auch nachweisen, indem eine Wiederholung der Dibenamin-Adrenalin-Belastungsprobe nach Genesung des betreffenden Patienten nun plötzlich erwies, dass die grosse Dosis einen eindeutig langdauernden Adrenalin-Hemmungseffekt, die kleine einen entsprechend geringeren und kürzer dauernden, der im übrigen normal gewordenen Nüchtern-Adrenalin-Belastungskurve zeitigte. Das passagere Versagen der grossen Dibenamindosis als Adrenalinhemmungseffekt, ja das Auftreten des Gegenteils, nämlich von Reizerscheinungen im Sinne der adrenergischen Verschiebung bei Dosen von 5 mg/kg Körpergewicht zeigten ebenfalls die gestörte Ausgangslage des Melancholikers. Denn hier treten Ef-

fekte schon bei einer Dosis auf, wie sie etwa beim normalen Menschen erst bei viel grösseren Dosen zu erwarten sind. (Es treten Reizerscheinungen auf, ja es kann zum Auftreten epileptischer Anfälle kommen.)

Wenn auch die Anzahl der Versuchspersonen noch gering erscheint, so verspricht das Dibenamin sich einen therapeutischen Anwendungsbereich in der Psychiatrie zu erobern; ferner gibt es interessante Einblicke in den Mechanismus vegetativer Pharmaca und ihr Zusammenspiel mit Erlebnismomenten.

Was nun die Dibenaminpsychose selbst betrifft, so darf an Hand der Literaturangaben und anderer eigener Versuchsserien etwa folgendes zusammengestellt werden: Bei Gaben von 4 mg/kg Körpergewicht aufwärts, treten in einem unter 20% liegenden Satz der Versuchspersonen bestimmte Veränderungen des Erlebens auf. Alle Versuchspersonen zeigen in mehr oder weniger starkem Masse vegetative Erscheinungen. Hierzu gehören Schwindelgefühl, gelegentlich Schwebesensationen, Blässe, Schwitzen, Müdigkeit, leichte Beklemmung und Kopfschmerzen, Brechreiz bis zu heftigem Erbrechen mit starker Nausea, conjunctivale Injektion, starkes Trockenheitsgefühl und schliesslich die bekannten Veränderungen in Puls, Blutdruck, Blutbild und Blutzucker.

Bezüglich der in etwa 20% auftretenden psychischen Symptome fanden wir den Beginn ihres Auftretens 10 Minuten nach Injektionsbeginn gelegen, wobei eine Injektionsgeschwindigkeit von 30 mg pro Minute eingehalten wurde. Diese Menge ist in 1 ccm. des Präparates enthalten und wird auf die vierfache Menge mit n/100 HCl angesäuerter physiologischer Kochsalzlösung verdünnt. In Zusammenfassung der objektiven und subjektiven Beobachtungen kommt es zu dieser Zeit zu einer leichten Bewusstseinseinengung und geringgradiger Bewusstseinstörung, einer Herabsetzung der Aufmerksamkeitsspannung sowie Verminderung der Vigilanz. Meistens ganz plötzlich tritt dann der Erlebnisbeiklang auf, alle Erlebnisinhalte seien nicht erstmals erlebt, sondern schon unmittelbar vorher vorhanden gewesen. Dieser Erlebnisbeiklang steigert sich zu Formen der absoluten Gewissheit, überhaupt nichts Neues mehr erleben zu können. Alles, was geschieht, ist eben vorher schon geschehen, ja vor diesem Vorher ebenfalls schon geschehen gewesen. Vom einfachen Wiederholungserlebnis steigert sich dieses bis zu absurden Zahlen: Eine unserer Versuchspersonen berichtete von über hundert Wiederholungen. Inhaltlich gesehen sind die Dinge, die sich wiederholen, kleinste Gedankengruppen, bzw. Erlebnisketten, Erlebniszyklen, wie z.B. (katamnästischer Bericht): "Ich lag auf dem Untersuchungsbett des Elektroencephalographen. Da ging die Türe auf, die Sekretärin betrat mit einem Stoss Bücher unter dem Arm den Raum, machte einen zögernden Schritt zurück und fragte: "Verzeihen Sie, darf ich rasch durchgehen?" um dann an mir vorbei auf den Zehenspitzen den Raum zu durchqueren und durch die andere Türe zu verlassen. Kaum war sie durch diese Türe verschwunden, als sie schon wieder, als wäre sie in einem 1/100000 Sekundenbruchteil durch den Raum zurückgefliegen, die erste Türe öffnete, mit einem Stoss Bücher unter dem Arm, einen zögernden Schritt zurück machte und fragte: "Verzeihen Sie, darf ich rasch durchgehen?", um dann an mir vorbei auf den Zehenspitzen den Raum zu durchqueren und durch die andere Türe zu verlassen. Doch im nächsten

Sekundenbruchteil betrat sie schon wieder durch die erste Türe den Raum und der ganze Vorgang wiederholte sich in minutiöser Präzision, wobei jeder ihrer Gesten und Bewegungen, sowie der Tonfall ihrer Stimme absolut gleich blieben. Das Ganze habe ich wenigstens 15 mal unmittelbar nacheinander erlebt."

Dabei ist der Bewegungsablauf der tatsächlich den Raum durchquert haben den Sekretärin in seinem Tempo ein absolut normaler und absolut normal erlebt worden. Objektiv gesehen sind die Patienten am Höhepunkt der Erlebnisstörung teilweise stuporös, bzw. kaum ansprechbar, teilweise ängstlich, ratlos, aber kontaktfähig, doch auch raptusartige Erregung kurzer Dauer wurde beobachtet.

Die Dauer dieser Erlebniszyklen, in der objektiven Zeitmessung gesehen, kann vom Sekundenteil bis etwa zu einigen Minuten reichen. Vom Standpunkt der subjektiven Zeit des Patienten werden sie einesteils als normaler Ablauf erlebt, andersteils in vielfacher Wiederholung aber doch nur den realen Zeitraum des Einzelerlebnisses beanspruchend.

Auch bei Versuchspersonen, die die Symptomatologie der Psychose vorher kannten und erwarteten, besteht ein absoluter Zusammenbruch des Realitätsurteils während der Erlebnisveränderung selbst, ja, sogar nach Abklingen der Psychose bedarf es eines förmlichen Sichdurchringens, um die Unmöglichkeit der Zeitverhältnisse einzusehen und immer wieder zu korrigieren, ebenso wie jene des Wiederholens.

Wir konnten an unserem Versuchsmaterial zeigen, dass die schon von Walther-Büel aufgestellte Vermutung der Zurückführung auf das *déjà-vu* sicher zutrifft. So berichtete ein Arzt, dass im Beginn der Störung ein typisches *déjà-vu*-Erlebnis vorgelegen habe. Bei einem unbedeutenden Hergang im Raume kommt plötzlich blitzartig der Gedanke: das war ja vor einer Weile schon da, vielleicht tritt die zu erwartende Wirkung jetzt ein. Von da an beginnt eine leichte Verwirrtheit und Unsicherheit, ob wirklich anormale Erlebnisse auftreten würden. Das Erlebnis, "Gott, das kenn ich ja schon, das war ja eben schon da", beginnt sich immer häufiger zu wiederholen, aber keineswegs bei allen wahrgenommenen Vorgängen. Beim Lesen von Zeitungsannoncen tritt fast immer die plötzliche Gewissheit ein, der Inhalt ist mir bekannt, wurde gerade vorgelesen. Später dann wird in diesem Moment aber auch schon die vermeintlich frühere Kenntnisnahme miterinnert, wie etwa: "Ja, auch damals habe ich schon gewusst, dass ich das eben schon gehört habe." Die Erinnerung an die vermeintliche Rückerinnerung tritt immer erst nach einer kurzen, aber deutlichen Zeitspanne auf, die sicher nicht gleich ist, und von den Versuchspersonen zwischen Bruchteilen einer und drei bis vier Sekunden geschätzt wird. Das Erlebnis hingegen der Bekanntheit als solches tritt unmittelbar mit der Wahrnehmung zusammen auf. Im Beginn gibt es Erlebnisse mit der unmittelbaren Wiederholungsgewissheit, die absolut unkorrigierbar bestehen bleiben und auch solche mit der Frage: habe ich das nicht schon gehört? Am Höhepunkt besteht jeweils sofortige Gewissheit der mehrmaligen Wiederholung.

Interessanterweise haben mehrere Versuchspersonen vom *déjà-vu* ausgehend im Beginn die Wiederholung auf 3-4 geschätzt, um dann am Höhepunkt der Wirkung nach etwa 30 Minuten auf Schätzung bis zu 50 und mehr zu kommen,

im Abklingen der Wirkung jedoch wieder schrittweise herunterzugehen bis zu 3 und 4. Über die Ursache des beschriebenen Phänomens gibt es nur Deutungen.

Für Dibenamin und das später zu besprechende Pharmakon Lysergsäurediäthylamid steht somit fest, dass es eine Veränderung im Gesamterleben des Menschen hervorzubringen vermag. Um nun einem Deutungsversuch der einmaligen Wirkung, dem Wiederholungserleben, näher zu treten, seien hier kurz die Ansichten der Voruntersucher diskutiert.

Rockwell dachte an eine Reizwirkung im Bereich des Temporallappens; dieser Anteil hat seinen eigenen Bau, der sich von dem der übrigen Hirnrinde unterscheidet. Er wird daher Allocortex genannt. Läsionen dieser Hirnregion führen zu den Abänderungen des Erlebens, wie sie unter dem Begriff der oneiroiden Erlebnisform oder dreamy states verstanden werden. Demnach würden alle in der Dibenaminpsychose auftretenden Symptome und somit auch das Wiederholungserlebnis nur Erscheinungsformen einer ihnen gemeinsam übergeordneten formalen Störung des Bewusstseinsablaufes sein, der Beziehungen zum epileptischen Geschehen hätte, bzw. als solches aufzufassen wäre. Es kommt zum Auftreten synchron entladender Zellgruppen, zu Rekrutierungsvorgängen in isolierten Bereichen ohne Anwachsen zu einer Synchronisation grosser Hirnteile. Dies führt zu vorübergehender funktioneller Abschaltung temporaler Hirngebiete.

Unsere elektroencephalographischen Untersuchungen an Dibenaminversuchspersonen konnten aber weder das Auftreten irgendwelcher epileptischer Manifestationen noch etwa speziell temporaler Spitzen aufzeigen; hiegegen spricht auch nicht, dass das Dibenamin in sehr grossen Dosen epileptogen wirkt.

Walther-Büel seinerseits ist geneigt, einen Teil dieser Wiederholungserlebnisse auf das déjà-vu zurückzuführen, wofür er den Namen "retrograde Reduplikationen" angewandt haben will. Doch glaubt er, dass es sich teils um nachhallende anschauliche Vorstellungen jüngster Vergangenheitserlebnisse handle, etwa einer Echovorstellung gleichzusetzen und prägte für diesen zweiten Mechanismus den Ausdruck der "anteretrograden Reduplikation," für die Störung den Ausdruck der "Echomnesie." Im Zusammenhang mit Beobachtungen über den Funktionskreis der Schlaf-Wachsteuerung glaubt er an ein Ergriffensein der funktionshöchsten vegetativen Apparate des Hirnstamms.

Während wir nun die Ansicht von Rockwell in Anbetracht der Unmöglichkeit, sie im Elektroencephalogramm zu verifizieren, nicht teilen möchten, kann jene von Walther-Büel nicht widerlegt werden. Wir fanden im Elektroencephalogramm eine Veränderung des Alpharhythmus, etwa wie folgt: Im Beginn der Dibenamin-Applikation normaler frequenzkonstanter Alpharhythmus occipita 10,5 c/sec., frontal 9,5 c/sec. bei normaler On-Off-Reaktion. 10 Minuten nach Beginn, zu einem Zeitpunkt, in dem subjektiv die ersten Symptome auftraten, Frequenzsteigerung auf 11 Herz. Während des Versuches in der folgenden Zeit (es wird mit Patienten gesprochen) unregelmässige niedrige Beta. 20 Minuten nach Versuchsbeginn lässt sich ein Alpharhythmus von 11 c/sec nur nach Lid-schluss nachweisen, 50 Minuten nach Beginn Höhepunkt der Wirkung, weiter 11 Herz Alpharhythmus.

Zusammenfassend lässt sich hier nur sagen, dass unter dem Einfluss des Medi-

kamentes eine Frequenzverschiebung des Alphasrhythmus geringen Grades nachgewiesen worden ist.

Demnach vermag das Electroencephalogramm keinen Aufschluss über die Mechanik der Dibenamin-Wirkung im einzelnen zu geben. Doch wäre in Parenthese zur Theorie der stroboskopischen Sehstörung vorstellbar, dass der normale Erlebnisablauf, der der Introspektion als Kontinuum erscheint, tatsächlich aus einer Folge von Erleben und Nichterleben, also einem cäsurierten Wellengeschehen besteht und hier unter dem Einfluss des Dibenamins jene Funktion blockiert wird, die für das pausenlose Ineinandergleiten der einzelnen Erlebnisakte verantwortlich ist.

Dieses Erleben der Dibenaminpsychose mit seiner geringen Veränderung im Electroencephalogramm steht im Gegensatz zu einer von Pötl und dem einen von uns (H.) beschriebenen Syndrom, dem Zeitraffer und dem Zeitlupenphänomen. Dieses spielt sich an optischen Sphären und zum Teil auch an der akustischen Sphäre ab. Hierbei kommt es zu einem Zustand, in dem der Patient alle Vorgänge im Sehraum richtig wahrnimmt, sie aber in einem völlig verändertem zeitlichen Ablauf erlebt; im Zeitrafferphänomen scheinen ihm alle Vorgänge mit rasender Geschwindigkeit abzulaufen, während sie im Zeitlupenphänomen wesentlich verlangsamt erscheinen. Während also in der Dibenaminpsychose das Individuum in einer gleichbleibenden Zeit die Vorgänge vielfach erlebt, spielen sich hier in einer ebenfalls gleichen Zeit die Vorgänge mit rasender Geschwindigkeit oder verlangsamt Tempo ab. Diese Vorgänge haben ein pathologisch anatomisches Korrelat, das von Pötl und dem einen von uns (H.) in Mechanismen der optischen Sphäre beschrieben worden ist und durch eine Störung thalamocorticaler Verbindungen bedingt erscheint. Bei diesen Störungen kommt es aber zu Veränderungen des Electroencephalogramms, während sie bei der Dibenaminpsychose vermisst werden. Es ist daher wohl anzunehmen, dass für das Zeitraffer- und Zeitlupenphänomen primäre Zerstörungen corticaler Gebiete verantwortlich sind, die für den richtigen Zeitablauf unserer Sinneswahrnehmungen notwendig sind, während bei den Dibenaminpsychosen offenbar ein Apparat in Unordnung gerät, der das Auslöschen alter Sinneseindrücke zur Aufgabe hat und von neuen Sinneseindrücken den Eindruck des schon Erlebten, schon Bekannten nehmen soll. Die geringe Veränderung im Electroencephalogramm spricht wohl dafür, dass dieser Apparat tiefen Hirnanteilen zugehört. Es wäre durchaus möglich, dass hier jener Apparat gestört ist, der mit dem Wach-Schlafmechanismus etwas zu tun hat.

Das Erleben im *déjà-vu* ist ja oft eng verknüpft mit dem des Traumhaften. Und nicht zu selten klingt ein Zustand der dreamy-states, wie wir sie bei Temporallappenläsionen finden, mit einem *déjà-vu* ab. Wir glauben, dass hier ein Übergang zwischen der Theorie von Rockwell und Walther-Büel gegeben ist. So konnte einer von uns (H.) zeigen, dass Reizungen im Bereich der hinteren Teile des Hypothalamus mit Aktionspotentialen im unteren Temporallappen beantwortet werden. Damit wäre eine funktionelle Verbindung der hinteren hypothalamischen Kerne mit dem Temporallappen gegeben, während als solche anatomischer Art nur Verbindungen von Uncus und Hippocampus zum corpus mamillare bekannt sind.

Die Analyse der Vorgänge bei der Dibenaminpsychose und jener des Zeitraffer- und Zeithupenphänomens führt somit zur Annahme zweier grundlegender, aber wesentlich verschiedener Funktionen:

Die Aufgabe der einen, wie sie im Zeitraffer- Zeithupenphänomen gestört erscheint, muss darin liegen, die Richtigkeit des zeitlichen Ablaufs in der Wiedergabe gesehener und vielleicht gehörter Wahrnehmungsinhalte zu garantieren. Der in der Dibenaminpsychose gestörte Mechanismus jedoch beinhaltet den Vorgang, neue Inhalte der Wahrnehmungswelt mit dem Stempel des Unbekannten, bzw. Neuartigen zu versehen, während eben Erlebtes, das schon den Stempel der Bekanntheitsqualität trägt, schon versunken sein muss, ehe ein Vergleich mit den Eindrücken der neuen Wahrnehmung zustandekommen kann. Bei der Störung dieses Vorgangs, also dem Verlust der Erlebniszäsur, würde dann die Nuance der Bekanntheitsqualität der im Erlöschen begriffenen Erlebnisinhalte mit hinübergenommen, bzw. transponiert werden auf die eben im Entstehen begriffenen neuen Wahrnehmungsinhalte und damit auch ihnen Bekanntheitsqualität verleihen.

Es ist interessant, dass der Apparat des hinteren Anteils des Hypothalamus, von dem wir annehmen, dass er etwas mit der Dibenaminpsychose zu tun hat, bei der Korsakoffschen Psychose am schwersten verändert ist. Wir wissen, dass gerade dieser Teil des Gehirns oft bei dieser Erkrankung von Blutungen durchsetzt erscheint. Beim Erinnern haben wir aber nicht nur das Auftauchen der alten Eindrücke, diese Eindrücke haben für uns auch schon die Qualität des bereits Erlebten, schon einmal Dagewesenen. Die nahe anatomische und funktionelle Verbindung der hinteren Anteile des Hypothalamus mit den medialen Anteilen des Thalamus machen es begreiflich, dass diese Erinnerungen oftmals mit emotionellen Tönungen verbunden sind, so dass das Erinnerungsbild mit den Vorzeichen des schon Erlebten, aber auch gleichzeitig mit dem Gefühl des angenehm oder unangenehm Erlebten besetzt ist. In diesem Sinne wird die Dibenaminpsychose, die manchmal die Komplikation therapeutischer Versuche sein wird, aufklärend auf eine Gruppe von psychischen Erscheinungen wirken, die unter dem Namen der Korsakoffschen Psychose oder Korsakoffähnlichen Psychosen zusammengefasst wird.

Während bei dem vorgenannten Pharmakon die einzigartige Wirkung auf den Erlebnisablauf als Besonderheit herausgehoben worden ist, ist dies bei der nun zu skizzierenden Erlebnisstörung des Lysergsäure-diaethylamids die unfassbare kleine Dosis, die bereits zu beträchtlicher Wirkung führt. 30 Millionstel Gram wurden als Durchschnittsdosis von Stoll und an unserer Klinik von A. Becker zu Versuchen an Menschen herangezogen. Abgesehen von vegetativen Störungen, wie allgemeines Krankheitsgefühl, Missbehagen, Hitze- und Kälteempfindungen, Brechreiz, Parästhesien usw. ist die Wirkung dieses Präparates gekennzeichnet durch die Trias: rauschartige Veränderungen, Wahrnehmungsstörungen mit Illusionierungstendenz und eigenartigen Störungen der Beziehung Objekt-Subjekt, bzw. Gegenstandsbewusstsein-Ichbewusstsein.

Insbesondere diese letztere Störungsgruppe hat eine unbestreitbare Ähnlichkeit mit einer bestimmten Erscheinungsreihe der schizophrenen Störung. Nicht so selten haben diese Patienten zunächst das Gefühl der Depersonalisation so, als

würden sie nicht selbst alle Dinge erleben, sondern gleichsam als Zuschauer dem Erlebnis ferne stehen. Schliesslich leitet dies über zum Gefühl, dass alles fremd und unwirklich sei, zum Gefühl, dass die Versuchsperson ihres eigenen Willens nicht mehr mächtig ist und dass ihre Gedanken gemacht werden. Hierher gehören auch noch die in Einzelfällen sehr stark in den Vordergrund tretenden Erlebnisse einer Umbewertung und Umbedeutung der existentiellen Masstäbe.

Wenngleich nun die Anwendungsversuche des Lysergsäureäthylamides im psychiatrisch klinischen Bereich noch spärliche sind, (Condrau) so haben sie doch ergeben, dass eine Störbarkeit der Erlebnisabläufe und auch des vegetativen Geschehens beim Psychotischen und insbesondere beim Schizophrenen entgegen den Erwartungen in viel geringerem Ausmass eintritt, denn beim Normalen.

Wir haben versucht, durch Anwendung von Lysergsäureäthylamid hebrephrene Prozesse umzustimmen und sie so vielleicht besser therapeutischen Massnahmen zugänglich zu machen. Es zeigte sich aber, dass beim Schizophrenen Störungen der Erlebnisabläufe und des vegetativen Geschehens entgegen unseren Erwartungen eben viel weniger ausgeprägt waren, als beim Normalen. Besonders interessant waren 2 Fälle, die beide anatomische Läsionen im Bereich des Zwischenhirns aufwiesen und bei denen trotz der wiederholten Anwendung von Lysergsäureäthylamid selbst in grossen Dosen keinerlei Reaktion auftrat. Dies ist umso überraschender, da wir ja bereits darauf hinwiesen, dass diese Droge in allen anderen Fällen wirkungsvoll war.

Die im Folgenden gezogenen Schlussfolgerungen seien mehr nach ihrer heuristisch-fiktiven, denn experimentell gesicherten Bedeutung hin aufgenommen. Schon die Tatsache, dass hier ein Spurenstoff so weitgehend über das gesamte vegetative System hin zur Auswirkung gelangte, ja schliesslich auch den gesamten Erlebnisvorgang des Menschen treffende Wirkungen auszulösen vermag, kann wohl nur mit der Tatsache erklärt werden, dass dieser Stoff in einem strengst spezifischen Sinn ein nur sehr eng begrenztes zellulär-morphologisches Substrat treffen kann; die weitgehende Ähnlichkeit der Lysergsäurewirkung mit einer bestimmten Symptomenreihe aus der Schizophrenie würde vielleicht weiter zu dem Schluss berechtigen, dass die gleichen am Erlebnisvorgang konstituierend beteiligten Faktoren auch von der schizophrenen Störung her affizierbar seien, unseres Erachtens aber noch nicht zu dem Schluss (siehe Condrau), dass die Psychose selbst durch einen ähnlichen Stoff hervorgerufen sein muss.

Was nun die Frage der möglichen Lokalisation dieses umgrenzten morphologischen Zellsubstrats betrifft, so dürfen unsere beiden hirnganischen Fälle mit Zwischenhirnläsion vielleicht herangezogen werden. Es wäre die Möglichkeit gegeben, dass bei diesen beiden Fällen die Zerstörung jener Kerngruppen vorliegt, an denen vor allen Dingen die Lysergsäurederivate ihren Angriffspunkt nehmen. Es wäre sogar vorstellbar, dass diese Kerngruppen beim schizophrenen Prozess funktionell erkrankt erscheinen. Dies soll aber keineswegs den Versuch bedeuten, die Schizophrenie als eine Diencephalose aufzufassen. Es wäre nur zu bedenken, ob nicht gewisse Symptome durch eine Dysharmonie in der Funktion dieser hypothalamischen Apparate in Bezug auf das übrige Gehirn erklärbar wären.

Schliesslich darf am Beispiel des Lysergsäuremechanismus das effektive Bestehen einer hierarchischen Rangordnung der funktionalen und morphologischen Substrate, also Zellverbände, abgelesen werden und die Berechtigung, zahlenmässig auch eng begrenzten Gruppen entscheidende Plätze und entscheidenden Einfluss auf die Gesamtfunktion des Seelischen zuzuerkennen (siehe etwa Penfield und Jaspers "Zentrum höchster Bewusstseinslage").

Um die Bedeutung experimenteller pharmakologischer Tätigkeit in der Therapie der Psychiatrie zu skizzieren, sei hier das Beispiel der modernen Muskelrelaxantia angeführt. Allen diesen Präparaten kommt eine Wirkung an der motorischen Endplatte zu, wenn auch zum Teil nicht nur an dieser. Die Wirkung an der Endplatte geht den Weg zweier Möglichkeiten:

Erstens den der Verhinderung der depolarisierenden Wirkung des Acetylcholins,

Zweitens den der dauernden Depolarisierung des Acetylcholins. Gruppe 1 darf, da dem Curare ähnlich wirkend, als Curarewirkungsgruppe bezeichnet werden. Sie ist charakterisiert durch die Antagonisierbarkeit mit Hilfe von Eserin. Ihr gehören zu:

a) die Tubocurarine

b) Synthetica, z.B. Flaxedil. Gruppe 2 summiert Stoffe, die nikotinähnlich wirken und durch Eserin nicht antagonisierbar sind. Hierher gehören

a.) Dekametonium (C 10)

b.) Lysthenon (M 115)

als Beispiel mit praktischer Bedeutung sei hier das Lysthenon (M 115) in seiner Anwendung bei einem psychiatrischen Therapieverfahren, dem Elektroschock herausgehoben, das erstmals von Ginzler und dem einen von uns (A.) in die psychiatrische Therapie eingeführt wurde.

Die Elektroschockbehandlung hat eine derart weitgehende Verbreitung gefunden, dass es berechtigt erscheint, die Frage der Komplikationen eingehend zu prüfen. Im Bereiche der möglichen Komplikationen spielen nun praktisch, wie folgende Tabelle (Eigenmaterial, A.) zeigt, (Tabelle 3) eigentlich nur jene an dem Skelettsystem auftretenden und hier in erster Linie die Kompressionsfrakturen der Wirbelsäule eine Rolle.

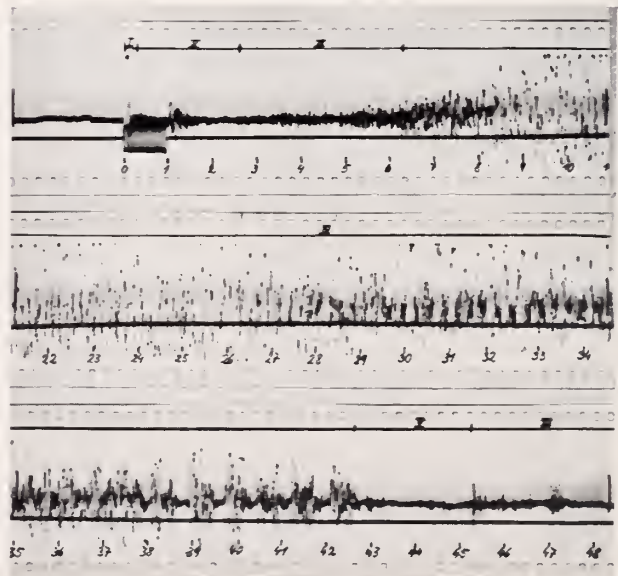
Um ihren Entstehungsmechanismus zu verstehen, scheint es notwendig, den Ablauf des Elektroschocks zu objektivieren. Hierzu wurde erstmals folgende Anordnung verwendet: Patient wurde auf einem Bett mit elastischem Einsatz gelagert und dieser Einsatz mit der Stirnfläche eines Herztonmikrophons verbunden, dessen Schwingungen mit Hilfe eines Philips Polycardiographen verstärkt und über Kathodenstrahlenschreiber registriert wurden (Tabelle 4). An Hand der so gewonnenen Kurven wurde in Übereinstimmung mit dem klinischen Bild des Schockablaufes eine Phaseneinteilung des Schocks und ihre zeitliche Festlegung vorgenommen.

Phase 1 = tonische Anspruchsphase, unmittelbar dem Stromschluss folgend, beinhaltet jenes blitzartige Zusammenzucken des Patienten, das unter Durchbrechung des Gesetzes der reziproken Innervation zur gleichzeitigen Innervation der hier vor allem interessanten Rückenstreck- und Rumpfbeuge (Bauchdecken)-Muskulatur führt.

TABELLE 3

KOMPLIKATIONEN DER L. ELTER 12 BEHANDLUNG									
Zahl d. Pat.	Männer	497	Frauen	200	697				
Zahl d. E.S.	(Anstalt)	497	(Klinik)	200	697				
Durchschnitt	8		6		7				
	Fall- zahl	E.S. %	Fall- zahl	E.S. %	Fall- zahl	gesamt P.Z., S., F., %	Weltlit P. %		
Chirurgische									
Schultergürtel	4	0,1	0,8	0		4 0,06	0,4 0,5		
Hüftgelenk u.						0			
Schenkelhals	0					0	0,8		
Wirbelsäule	43	1,07	8,6	16	7,53	59 0,84	5,9 8-25		
Interne									
Atemstörung	2	0,05	0,4	0		2 0,03	0,2 0,2		
Herz-Kreisl.	5	0,12	1,0	2	0,06	7 0,1	0,7 1-3		
Aspirations- pneumonie	4	0,1	0,8	2	0,06	6 0,06	0,6 1?		
Todesfälle	2	0,05	0,4	1	0,05	3 0,03	0,3 1?		
Lungenabszess	3	0,07	0,6	0		3 0,03	0,3 1?		
Todesfälle	1	0,03	0,2			1 0,01	0,1 1?		
Gesamtzahl der Todesfälle							0,4 %		
Psychiatrische									
"Uranget"						ca 0,0	?		
Dämmerzustand						ca 3,0	?		
Korsakoff	2	0,05	0,4	0		2 0,03	0,2 ?		
Neurologische									
Purpura cerebri						zwei Todesfälle			
Epilepsie	4	0,1	0,8	2	0,06	6 0,06	0,6 1 ist g		
						1 Satz d. Bevolk.			

TABELLE 4



Phase 2 entspricht dem stillen Latenzstadium, das dann in

Phase 3, das eigentliche tonische Stadium übergeht.

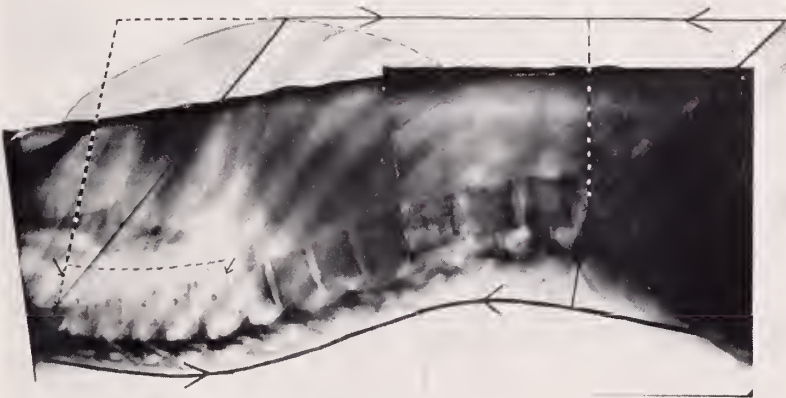
Phase 4 = das Stadium der Klonismen;

Phase 5 = jener Zeitraum, der dem Aufhören der Klonismen folgt und durch absolute Asphyxie gekennzeichnet ist und schliesslich den Schockausklang beinhaltet.

Die klinische Annahme, gestützt durch röntgenologische Untersuchungen, ist nun die, dass die Wirbelfraktur der Gleichzeitigkeitsimmervation der tonischen Anspannungsphase zuzuschreiben ist.

Die folgende Montage (Tabelle 5) zeigt den Verlauf der Wirbelsäule eines flachgelagerten Patienten: aus ihr geht hervor, dass bei Anspannung der Erector-Trunci-Gruppe (siehe Pfeile der unteren Linie) es zu einer maximalen Annäher-

TABELLE 5



ung der Wirbelkörper kommt. Die gleichzeitige Anspannung der, wie eine Sehne über lange Hebelarme angreifenden und trotz ihrer geringen Quantitäten enorm wirksamen Bauchmuskulatur erzielt hiezu noch eine Kippbewegung nach vorne. Das Resultat dieser beiden Energien kann dann mehr oder weniger ausgedehnte Frakturierung, bzw. Kompression des von der Kippbewegung nach vorn am stärksten betroffenen Wirbelsäulenanteils sein, das ist der Bereich des 4. bis 8. Brustwirbels. Dies sind nun tatsächlich die Prädilektionsstellen der Schockfraktur. Unterstützend wirkt hiezu noch die bei normaler Rückenlage präformierte Annäherung der Wirbelvorderkanten dieses Bereiches.

Es bestehen klinische und biochemische Anhaltspunkte, dass es für die Wirkung eines Elektroschocks nicht gleichgültig ist, ob eine Reaktion der Peripherie stattfinden kann oder nicht. Die dem physiologischen Mechanismus des spontanen epileptischen Anfalles adaequate, dosierte Muskelarbeit der gesamten Körpermuskulatur stellt eine ungeheure Reizverschiebung in der Peripherie dar. Wir

glauben, dass man grundsätzlich nicht das Rückmeldeprinzip Peripherie-Zentrum durchbrechen und auf das Mitarbeiten der Peripherie verzichten darf, wenn der Schockeffekt nicht zum Teil paralysiert werden soll.

Die Forderung an ein modernes Muskelrelaxans für E-schock-behandlung, lautet daher:

1. Keine Atmungs- oder Kreislaufbedrohung,
2. Absolut sichere Mitigierung der tonischen Anspruchsphase des Elektroschocks,
3. Keine Behinderung der dann folgenden, für das Skelettsystem gefahrlosen Klonismen.

Ausschliesslich ein Präparat, dessen Wirkung im Zeitablauf diesen Anforderungen entspricht, hat Berechtigung, zu einer Standardmethode herangezogen zu werden. Die folgende Elektromyogrammkurve Tab. 6 zeigt die Wirkung des M 115 im optimalen Zeitdosierungsschema, das wie folgt lautet: 0, 1 mg/kg Körpergewicht in halbprozentiger Lösung in genau 10 Sek. i.v. zu applizieren. Der erste Teil des Elektromyogramms zeigt in der oberen Kurve neben dem eingestreuten Elektrokardiogramm Aktionspotentiale der Atemmuskulatur, der untere Teil Aktionspotentiale der Bauchdeckenmuskulature beim Befehl Kopfhoben, die dritte Marke zeichnet den Befehl Kopfhoben. Die anschliessende Kurve (Tabelle 6) lässt einen Zeitmasstab (arabische Ziffern) in Sekunden erkennen. Die erste Markierung über 10 Sekunden bedeutet die Injektionszeit, die Sekundenskala läuft nun vom Ende der Injektionszeit weiter. Deutlich ist in der Ableitung der Atemmuskulatur (erste Linie) zu sehen, wie die Muskelaktionen etwa ab der 15. Sekunde weitgehend verschwinden, aber schon etwa nach der 58. Sekunde wieder aufzutreten beginnen, das heisst, wie auch Elektromyogramme anderer Ableitung bewiesen: 60 Sekunden nach der Applizierung des Mittels in dieser Form ist seine atembehindernde Wirkung weitgehend abgeklungen.

Die zweite Linie zeigt, dass Patienten den Befehl Kopfhoben wohl nach 9 Sekunden noch nachkommen können, dass die weiteren Befehle des Kopfhobens aber an der muskelrelaxierenden Wirkung des Präparates scheitern und erst in der 65. Sekunde wieder Aktionspotentiale der Bauchdeckenmuskulatur nachgewiesen werden können.

Die folgende Tabelle (Tabelle 7) zeigt eine nicht wirkungsmassstabgerechte, schematische Skizze, deren zeitliche Verhältnisse aber präzisiert sind. Die obere Kurve beinhaltet die muskelrelaxierende Wirkung auf die Skelettmuskulatur, die untere Kurve die atembehindernde des M 115 und die atembehinderte (rechte Bildseite) der Schockphase 5. Wenn der Elektroschock genau 30 Sekunden nach Ende der Applikation des Mittels gesetzt wird, so wird damit erreicht:

1. Die tonische Anspruchsphase kommt in den Höhepunkt der muskelrelaxierenden Wirkung in Bezug auf die Skelettmuskulatur.
2. Zu diesem Zeitpunkt ist die Wirkung auf die Atmung bereits im Rückgang.
3. Die Tonische Phase des Krampfes wird noch voll getroffen, die folgende klonische (Phase 4) jedoch nur mehr teilweise, gegen Ende haben die Klonismen wieder völlige Stärke erreicht.
4. Im Zeitpunkt der apshyktischen Schockphase (Phase 5) ist die atembe-

TABELLE 6

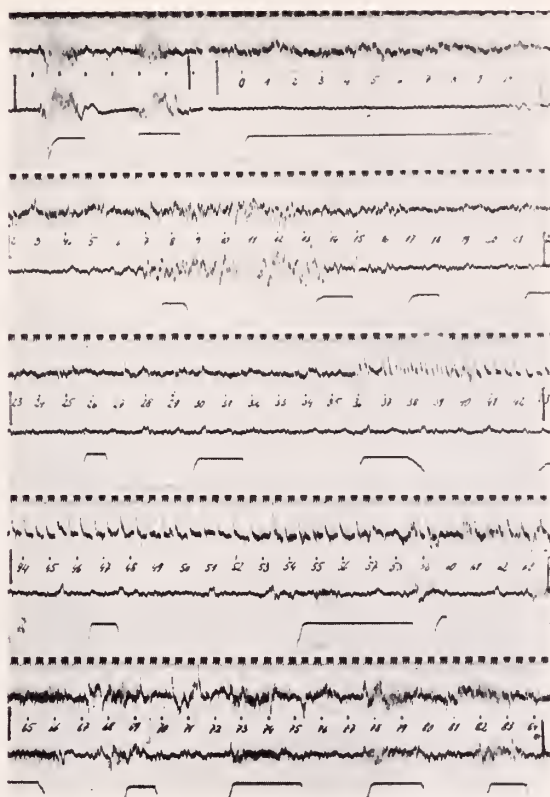
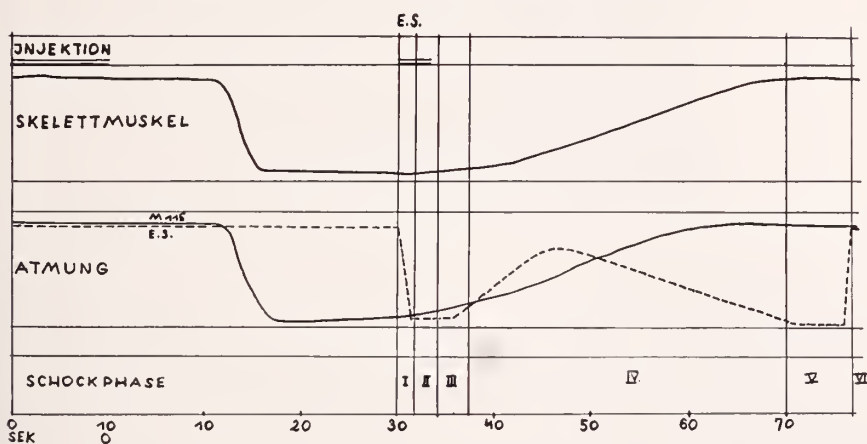


TABELLE 7

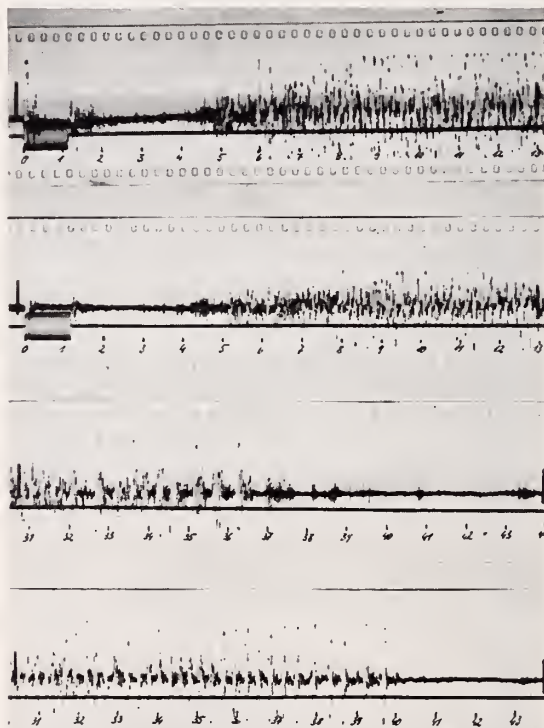


hindernde Wirkung des Medikamentes bereits verschwunden und damit eine Kumulierung mit der Phase 5 absolut unmöglich.

Die nächste Kurve (Tabelle 8) zeigt, wieder mit Hilfe der Betteinsatz-Herzton-

Registrierung, den Vergleich des Schockablaufs ohne und mit M 115. Es wurden hier ohne Veränderung der Lagerung am gleichen Patienten nacheinander 2 Versuche registriert. Die Mittelteile der Kurven wurden aus Reproduktionsgründen weggelassen. Kurve 1 setzt sich in der 3. Reihe, Kurve 2 in der 4. Reihe fort. Um den Unterschied zu verstehen, muss man bedenken, dass die Grösse der Energieübertragung der vom Patienten während des Schocks geleisteten Muskelarbeit auf das schwingende Bett sowohl in Amplitudenhöhe als auch in der Dämpfungszeit (Dauer der Nachschwankungen) zum Ausdruck kommt. So ist hier eindeutig zu sehen, dass die tonische Anspruchsphase zu ihrer Dämpfung

TABELLE 8



fast eine halbe Sekunde bedarf, wenn Patient ohne M 115 geschockt wurde, während in der zweiten Kurve (mit M 115) die tonische Anspruchsphase ausschliesslich durch ein kurzes Anschwingen mit sofortiger Dämpfung registriert wird. Die Vergleiche der Enden der Kurve dagegen zeigen die Gleichheit der Klonismen mit und ohne M 115. Ferner ist rechts über den Sekunden 43 an den kleinen Ausschlägen in beiden Fällen das spontane Wiederingangkommen der Atmung ablesbar.

Es konnten mit dieser Methode bis jetzt 120 Patienten insgesamt 532 mal ohne den geringsten Zwischenfall von Seiten des Skelettsystems oder der Atmung geschockt werden.

Dem M 115 kommt in dieser Dosis keinerlei Wirkung auf Herzkreislauf zu.

Unter diesen Patienten fanden sich nicht weniger als 12 (10%) mit solchen Veränderungen des Skelettsystems, die eine Behandlung ohne M 115 unmöglich gemacht hätte, da gleichzeitig bei ihnen teils kreislaufdynamische, teils anatomische Behinderungen der Atemfunktion beträchtlichsten Ausmasses bestanden. Unter anderem wurden 2 Fälle frischer Wirbelfrakturen, 3 Fälle mit schwerster Kyphoskoliose (Alter zwischen 66 und 78) und ein Fall einer frischen Schenkelhalsnagelung komplikationslos einer mehrfachen Elektroschockbehandlung unterzogen.

Die Entwicklung dieses Präparates darf als ein Beispiel der Arbeit experimenteller Pharmakologie (Pharmakologisches Institut der Universität Wien, Professor Dr. Brücke), seine Heranziehung zur Elektroschockbehandlung als ein Beweis der notwendigen Zusammenarbeit zwischen experimentellen Pharmakologen und Kliniker angeführt werden.

So hoffen wir gezeigt zu haben, wie weitgehend gerade die experimentelle Pharmakologie unsere moderne Psychiatrie beeinflusst. Schon sind wir imstande, die Ergebnisse in der Therapie der Patienten zu verwenden. Sie helfen uns aber auch, Mechanismen in den psychischen Erkrankungen der Patienten zu verstehen und ein besseres Verstehen scheint uns ein mächtiger Schritt vorwärts auf dem Wege zum Ziel rascher Heilung dieser oft prognostisch noch so ungünstigen Erkrankungen. Wird dies in künftiger Zeit der Fall sein, so wird es nicht zum geringsten das Verdienst Ernst Peter Picks sein, dessen Geist in seinen Schülern, in seinem Institute und in seiner Vaterstadt weiterwirkt.

SUMMARY

(1) The authors discuss at some length the changes in the usual reaction to dibenamin when given to patients in states of depression. This is explained by a disturbed equilibrium within the vegetative nervous system with preponderance of the parasympathetic division. Small doses of dibenamin are effective while large ones fail. The so called dibenamin psychosis is discussed in some detail and related to the *déjà-vu* sensation. Electroencephalographic studies fail to substantiate Rockwell's theory of the dibenamin psychosis. An attempt is made to correlate previously described (Pötzl, Hoff) disturbances of the sensation of time and their morphological substrate with the dibenamin psychosis. Functional connections between the posterior part of the hypothalamus and the temporal lobe which were demonstrated by Hoff may reconcile the divergent explanations of dibenamin psychosis of Rockwell and Walter-Büel. The posterior hypothalamus is also involved in Korsakoff type psychoses pointing to a common denominator of *déjà-vu* sensation on one hand and disturbed memory on the other.

(2) Lysergic acid diethylamid given in 30 gamma (γ) doses produces a series of psychological effects among which depersonalisation and related impressions are worthy of note because of their occurrence in schizophrenia. The conclusion that this disease is caused by a similar chemical compound is, however, unjustified at present. Of interest is the finding of two cases of tolerance to this powerful drug, both of which showed morphological alterations in the diencephalon.

(3) Recent advances in our knowledge concerning agents that paralyze skeletal

muscle added to the safety of electro-shock treatment by eliminating many contra-irradiations particularly on the part of the osseous system (compression fractures of spine). The pharmacology of the agents of this group is discussed. Studies of tracings obtained by a refined technique enable one to divide the electric shock into five distinct phases. Only the first one which is characterized by synchronous innervations of erector trunci and abdominal wall muscles, is of danger to the patients spine. The phase of clonic convulsions is harmless for the skeleton and therapeutically desirable. A new quick acting drug (M 115) interferes with the tonic phase thus protecting the patients spine. The electric shock when given exactly 30 seconds after the injection will thus be modified. In addition, any depressing influence the drug has on respiratory centers will not coincide with the fifth (asphyctic) phase of the electro shock.

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FIXATION OF COMPLEMENT WITH THE PURIFIED FACTOR IN MOUSE MILK CONNECTED WITH MAMMARY CARCINOMA*†

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As far as the writers are aware, there has been no prior publication of data on the fixation of complement by known weights of a virus pathogenic for animals and known weights of homologous antibody. While the viral nature of the factor (F) in mouse milk connected with mammary carcinoma is still under discussion, the purified material isolated according to (1) is a readily sedimentable particle, of weight approximately 300×10^6 , and is strongly antigenic in rabbits with the production of precipitating antisera (2). It may therefore serve as a model, at least, for virus anti-virus interaction.

Rabbit antisera to F not only precipitate F (2) but also fix complement with the antigen at high dilutions. The accompanying table illustrates some of the data obtained.

The antisera in the table were successive bleedings of a rabbit given three injections intramuscularly at weekly intervals with a mixture of F, Aquaphor, mineral oil, and tubercle bacilli. The bleeding designated by the subnumeral 1 was taken ten days after the last injection, the others at the intervals given.

Final dilutions of F and of antisera were made with veronal-Mg⁺⁺, Ca⁺⁺ buffer (3). Test mixtures of antigen, antibody, and 1.5-100 per cent hemolytic units of guinea pig complement were made up to 0.6 ml., incubated at 0-5° C overnight, mixed with 0.2 ml. of sheep cell-hemolysin mixture (4) and incubated at 37° C for an additional 30-45 min. Readings range from 0, no hemolysis, to 4, complete hemolysis.

It will be noted that fixation of complement occurs at levels of antigen and antibody not greatly different from those previously observed (5, 6). The sensitivity of the test with F does not appear to extend to such small quantities of antigen as, for example, in the case of bovine serum albumin (6), an antigen of much smaller molecular weight which would contain about five thousand times as many molecules in the same weight of nitrogen. Per microgram of serum albumin the number of molecular groupings capable of reacting with antibody and complement would probably be several orders of magnitude greater than in the case of F.

It was perhaps to be anticipated, also, that the successive bleedings would show the pattern of complement fixation characteristic of the first course bleeding in (6, Table III), since no additional courses of injections of antigen were

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given. It will be recalled that in (6) differences were noted in the patterns of complement fixation in sera taken after a single course of injections of antigen and those collected after a subsequent course.

TABLE 1

Fixation of complement by mouse milk factor and rabbit antisera to the purified substance

MICROGRAMS FACTOR NITROGEN	MICROGRAMS ANTIBODY NITROGEN IN TEST			
	0.2	0.1	0.04	0.02
Antiserum 10 ₁ , 7/18/49, 109 μ g antibody N/ml.				
0.5	0	0	0	3½
0.25	0	0	0	4
0.125	0	0	0	4
0.05	1	2	4	4
0.025	3½	4	4	4
0.0025	4	4	4	4
Antiserum 10 ₂ , 8/11/49, 95 μ g antibody N/ml.				
0.5	0	0	½	4
0.25	0	0	½	4
0.125	0	0	½	4
0.05	1	3	3½	4
0.025	4	4	4	4
0.0025	4	4	4	4
Antiserum 10 ₃ , 9/6/49, 78 μ g antibody N/ml.				
0.5	0	0	3	4
0.25	0	0	1	4
0.125	0	1	1	4
0.05	2	2	4	4
0.025	4	4	4	4
0.0025	4	4	4	4
Antiserum 10 ₄ , 10/18/49, 25 μ g antibody N/ml.				
0.5		0	0	4
0.25		0	0	4
0.125		0	½	4
0.05		1	3½	½
0.025		4	4	4
0.0025		4	4	4

Results were similar with another preparation of milk factor.

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ISOTOPICALLY LABELED NIRVANOL¹

HARRY SOBOTKA, PH.D. AND F. E. STYNLER, PH.D.

More than twenty years ago, Sobotka, Holzman, Kahn, Peck and Schick (1, 2, 3) demonstrated that the drug eruption known as "Nirvanol disease" was primarily due to the levorotatory form of 5,5-phenylethylhydantoin. Nirvanol disease is a generalized morbilliform eruption accompanied by fever, which breaks out 9-12 days after the first administration of the drug Nirvanol, 5,5-phenylethylhydantoin. Other less frequent symptoms of the disease are joint pains, swollen ankles and eyelids and other signs of edema, occasionally anuria and other disturbances of a more severe nature. Nevertheless, the drug was for many years widely given, especially to children with Chorea Minor. During this time the pediatricians, well aware of the beneficial effects of Nirvanol, could not agree among each other, whether Nirvanol acted like any other sedative and produced "Nirvanol disease" as an undesirable side-effect in a high number of instances, or if the fever temperatures of this drug eruption were in themselves of beneficial nature to the patient. Since then, we have learned to bring about both effects by other means separately from each other.

When our attention was first drawn to Nirvanol and "Nirvanol disease," we separated the compound into its two enantiomorphic components and found that the levorotatory form was pharmacologically slightly more active than the dextrorotatory form, but that it was almost exclusively responsible for the production of Nirvanol disease. The incubation period of about ten days following the first administration strongly suggested analogy with serum sickness. We assume that the hydantoin ring of Nirvanol is opened during the processes of catabolism and that the resulting phenylethylglycine is incorporated into some of the protein molecules of the human body, there to act as antigen and to elicit antibody production. This hypothesis requires some qualifications: first, that the antigenic amino acid must be present in *statu nascendi*, since the amino acid, prepared in vitro, does not produce effects of this nature; second, that either the antigen or the antibody must be bound in the peripheral tissues where the reaction can become manifest at the end of an incubation period. This then would be the working hypothesis, namely, that the drug is split during its degradation in the animal body into an amino acid or closely related derivative which attaches itself in *statu nascendi* as a "spontaneous haptene" to some protein of the body. From there on, it acts like a foreign protein, brought into circulation, and produces those allergic symptoms which are typical for its nature and for the nature of the host.

We had learned from our experiments that the skin eruption could not be produced in rats, guineapigs or rabbits. The number of children with Chorea Minor and similar seizures has considerably decreased during recent years and the amounts that could be given to an individual are of course limited. We therefore seized the occasion, when N¹⁵ and C¹⁴ became commercially available after the

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end of the war, to resume the work with these new tools. It should now be possible to study the fate of the antigen in human and animal body by actually following the drug from the moment of its administration.

We describe in the following two methods which were tested for introducing N^{15} into position "1" of the ring of 5,5-phenylethylhydantoin.

The first method tried was that of Bucherer (4, 5) and of Henze (6, 7, 8). In contrast to the older methods it consists of a single step; the ketone, in the present case propiophenone, is condensed with potassium cyanide and ammonium carbonate. Bucherer assumes the primary formation of the aminonitrile, $R_1R_2C(NH_2)CN$, as in Strecker's synthesis of amino acids, and then stepwise addition of carbon dioxide and ammonia towards hydantoic acid and possibly dimeric intermediates, followed perhaps by amide formation and cyclization with elimination of the third nitrogen atom. There is no reference to the exact nature of the ammonium carbonate.

Henze refers in several places specifically to "cubes" of ammonium carbonate. Now, according to the 24th edition of the U. S. Dispensatory (9) "ammonium carbonate consists of ammonium acid carbonate (NH_4HCO_3) and ammonium carbamate ($NH_2 \cdot COO \cdot NH_4$), in varying proportion, and yields not less than 30% and not more than 33% of NH_3 ." "... At present the salt is manufactured by heating a mixture of ammonium chloride and calcium carbonate in iron pots or retorts; the ammonium carbonate vapor is condensed and the ammonia vapor is conducted into an acid solution." (cf. 10)

Mixtures of bicarbonate and carbamate with 30–33% ammonia would be composed as follows:

30% NH_3	71.6% bicarbonate and 28.4% carbamate
33% NH_3	55.8% bicarbonate and 44.2% carbamate.

Bucherer seems to consider commercial ammonium carbonate as a mixture of carbamate with neutral carbonate both of which he shows in structural formulas (4). Such a mixture could not yield a product within the NH_3 -limits of the U. S. Dispensatory and Pharmacopoeia, since either component contains more than 33% ammonia. In several examples Bucherer specifies ammonium carbamate. Henze, on the other hand, usually writes "ammonium carbonate", but in some instances specifies "cubes" and evidently accepts the official definition for it.

According to Henze the method is best carried out by heating together one equivalent of the ketone, one and one-quarter equivalent of potassium cyanide, and four and one-half equivalents of ammonium carbonate for 10 hours to 58–60°. Higher temperatures lead to loss of ammonium salts by sublimation. After cooling, the pH is brought down to ca. 4.0 by addition of hydrochloric or sulfuric acid and, after most of the alcohol has been blown off, the substance crystallizes.

Our own experiments, which are summarized in Table I, were carried out with fresh cubes. The propiophenone boiled at 62° under 1.5 mm. Hg pressure and had $n_D^{20} = 1.5256$. The yield of Nirvanol, calculated on the ketone, was not af-

fectured by any amounts of ammonium carbonate beyond the ratio of 1.75 to 1 equivalents, but receded at lower proportions of the ammonium salt. Calculating the yield however on the ammonium carbonate, the ratio 1.75 to 1 was optimal as seen in the last column of Table I. The maximum yield of 26.6%, as calculated on the ammonium salt, would be tolerable, especially if the unreacted ammonia could be recovered. In reality, it can not be recovered. But, what is decisive, the "ammonium carbonate U.S.P." can not be produced on the small scale imposed by the high price of heavy nitrogen.

TABLE I

Synthesis of phenylethylhydantoin from 10 gms. propiophenone, 6.1 gms. potassium cyanide (1.25 eq.) and varying amounts of "ammonium carbonate" cubes in 250 ml. 70% ethanol

AMMONIUM CARBONATE GMS.	MOL. PROP. AMMONIUM CARB.: PROPIOPHENONE	YIELD		
		Gms.	% Calculated on Propiophenone	% Calculated on Ammonium Carbonate
26.5	4.5 :1	6.6	43.4	9.5
11.8	2 :1	6.4	42.1	21.5
10.3	1.75:1	7.1	46.6	26.6
8.8	1.5 :1	4.6	31.2	20.1
5.9	1 :1	0	0	0

TABLE II

Composition of ammonium carbonate cubes

	CONTENT OF NH ₃	SAMPLE A		SAMPLE B	
		% of Component	% NH ₃	% of Component	% NH ₃
Ammonium carbamate.....	43.6	35.5	15.5	22.5	9.8
Ammonium carbonate.....	35.4	6.0	2.1	29.5	10.6
Ammonium bicarbonate.....	24.6	58.5	14.4	48.0	11.5
Total		100.0	32.0	100.0	31.9

We tried, therefore, to decide which component of the cubes was essential to the success of the synthesis. Ammonium carbamate may be separated by ethanol which dissolves it, leaving the acid and neutral carbonates behind. Two batches of cubes, each analysed in duplicate, gave the results summarized in Table II. The carbamate was determined by alcoholic extraction for 2 hours in a closed round flask with mechanical stirring, filtration and evaporation. The distribution of the remainder between bicarbonate and carbonate was calculated on the basis of the ammonia content. The specimen designated "B" had been standing in the laboratory for more than a year and was no more translucent. It may be assumed that specimen "A" approaches the analysis of the fresh product which actually may be a purely binary mixture of carbamate and bicarbonate. The cubes used in the synthesis experiments were from a fresh batch; they had a translucent appearance with only superficial efflorescence.

The individual components were tried in several experiments. The examples given in Table III show that neither the alcoholic solution of a given amount of carbamate nor mixtures of carbamate with bicarbonate were useful in the synthesis. Pure ammonium bicarbonate, which is commercially available in C.P. grade, did not give satisfactory yields either. Thus, we decided to use a combination of older methods for our purpose.

The most favorable series of reactions would start with benzyl cyanide (phenylacetonitrile) into which one would introduce in two steps the carboxethyl and the ethyl group; the ester would be converted into the amide and the resulting disubstituted cyanoacetamide rearranged and cyclized to the hydantoin.

Thus, benzyl cyanide was reacted in the presence of sodamide (11, 12) with ethyl carbonate, giving a yield of 45% of the theory of the ethyl ester of phenylcyanoacetic acid. In order to make the most economical use of N¹⁵, we attempted to introduce it as late as possible in the series of reactions, thus, we inserted as the next step the ethyl group by reacting the ester with ethyl iodide in the presence of sodium ethylate. The reaction yielded the ester of phenylethyl-

TABLE III

Synthesis of phenylethylhydantoin from 10 gms. propiophenone, 6.1 gms. potassium cyanide and various ammonium salts

	GMS.	MOL. PROP. AMMONIUM SALT: PRO- PIOPHENONE	YIELD		
			Gms.	% Calculated on Propio- phenone	% Calculated on Ammonium Salt
Ammonium Carbamate.....	10.2	1.75:1	0	0	0
Ammonium Bicarbonate.....	11.8	2 :1	2.7	17.7	8.8
Ammonium Carbamate....	5.8}	1.75:1	0	0	0
Ammonium Bicarbonate..	4.5}				

cyanoacetic acid in 70% yield. However, this ester which carries no more H-atom on the central carbon atom can not be amidated. We therefore followed the outline of Chem. Fabrik von Heyden A. G. (13), who recommend amidation before ethylation. This amidation was carried out according to J. C. Hessler (14) by distilling concentrated ammonia into the aqueous suspension of the ethyl ester of phenylcyanoacetic acid. The reaction led to the amide in 62% of theory, which was then ethylated in 87% yield with ethyl iodide. The resulting phenylethylcyanoacetamide was then subject to oxidative ring closure with sodium hypobromite; yield up to 91%. This Hofmann rearrangement must be performed under the special precautions given in Organic Reactions (15). The resulting phenylethylhydantoin melted at 201°.

The process was then duplicated with the use of heavy nitrogen (31.9 atom % excess N¹⁵) as ammonium nitrate, labeled on the ammonium nitrogen, in the amidation step. The end product melted at 202–203° after several recrystallizations from aqueous ethanol.

Anal. Calcd. for C₁₁H₁₂O₂H₂ (with due allowance for N¹⁵): C, 64.59; H, 5.92; N, 13.85. Found: C, 64.74; H, 5.64; N, 13.95.

Its N^{15} content was determined mass-spectrographically as 15.9 atom % excess N^{15} , only one of the two nitrogens in the molecule being labeled. The location of the heavy isotope in position "1" of the ring was proved by acid hydrolysis when the resulting phenylethylglycine contained 31.6 atom % excess N^{15} , whereas the ammonium sulfate had only traces amounting to 0.009 atom % excess N^{15} . The Nirvanol so labeled is now being used for an investigation of its fate upon administration to animals.

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EFFECT OF SOME REAGENTS ON THE FLUORESCENCE OF STILBAMIDINE AND 2 OH-HYDROXYSTILBAMIDINE IN VITRO*

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It is well known that the fluorescence of 2-hydroxystilbamidine *in vitro* is strongly increased by ethanol or an ethanol-ether mixture 9:1 (1).** It is shown in the following that an increase in the fluorescence of this substance as well as of stilbamidine is brought about also by CH₃OH, acetone and glycerol.

All these reagents are in use for the fixing and preparation of organ sections for microscopic examination. The cell nuclei of human and animal tissues, treated with 2-hydroxystilbamidine, exhibit a strong fluorescence when fixed with one of the reagents mentioned. However, this is not or hardly the case in tissues of animals receiving stilbamidine. This could be explained by two assumptions: a) only the hydroxy-derivative is able to penetrate into the nuclei; b) both amidines penetrate into the nuclei, but the fluorescence of stilbamidine is suppressed by the presence of nucleic acids, as has been described in this laboratory (2). Nucleic acids lower the fluorescence of stilbamidine *in vitro* while they increase the fluorescence of 2 OH-stilbamidine. It is shown in the following that nucleates *in vitro* are in fact able to overcome nearly completely the increase of stilbamidine fluorescence due to ethanol and acetone, but that their effect on the strong increase, due to glycerol, is a much smaller one. Thus, if after treatment with stilbamidine, tissue samples mounted in glycerol show no fluorescence in the nuclei, it would be highly probable that stilbamidine is absent from these structures. This would invalidate the assumption b).

RESULTS

A. Stilbamidine

Stilbamidine diisethionate (Merck) in 10 mg. per cent aqueous sol.

Sodium nucleate (Schwarz Labs., N. Y.) in 30 mg. per cent aqueous sol.

All samples are filled to 25 cm³ with water or glycerol etc.

I)

cm ³ :	Stilbam.	Na nucl.	Etha no ¹	Acetone Merck	Glycerol, Merck		Fluorescence readings (on Lumetron)
1)	1	—	—	—	—	Filled with H ₂ O to 25 cm ³ .	set at 50
2)	1	2	—	—	—	" "	13.3
3)	1	—	12	—	—	" "	> 100
4)	1	2	12	—	—	" "	19.5
5)	1	—	—	—	Filled to 25 cm ³ .	—	beyond scale!
6)	1	2	—	—	" "	—	" "
7)	—	2	—	—	" "	—	13.0

* From the Second Medical Service of Dr. I. Snapper, The Mount Sinai Hospital, New York, N. Y.

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** In this reference the method is applied to propamidine and pentamidine.

II) With different amounts of ethanol and acetone:

1)	1	—	—	—	—	“	“	set at 50	
2)	1	—	8	—	—	“	“	92	89.2
3)	1	—	16	—	—	“	“	> 100	> 100
4)	1	—	24	—	—	“	“	≥ 100	≥ 100
5)	1	2	—	—	—	“	“	14.6	7.0
6)	1	2	8	—	—	“	“	22.9	15.2
7)	1	2	16	—	—	“	“	22.8	15.7
8)	1	2	22	—	—	—	—	21.3	8.6
9)	1	—	—	8	—	“	“	86.4	
10)	1	—	—	16	—	“	“	91.5	
11)	1	—	—	22	—	“	“	> 100	
12)	1	2	—	—	—	“	“	9.6	
13)	1	2	—	8	—	“	“	15.2	
14)	1	2	—	16	—	“	“	10.5	
15)	1	2	—	22	—	—	—	3.5	

In the presence of alcohol or acetone without nucleates the fluorescence of stilbamidine increases with increasing amounts of these reagents; when nucleates are added, there is first an increase and then a decrease of fluorescence.

III) With different amounts of glycerol:

cm ² .	Stilbam.	Na nucl.	Glycerol		Filled with H ₂ O to 25 cm ³ .	Fluorescence readings	
			I	II		I	II
1)	1	—	—	—		set at 50	
2)	1	—	8	5	“	> 100	80.5
3)	1	—	12	10	“	≥ 100	> 100
4)	1	—	16	15	“	beyond scale!	
5)	1	2	—	—	“	1.0	7.3
6)	1	2	8	5	“	40.2	19.2
7)	1	2	12	10	“	71.9	54.6
8)	1	2	16	15	“	≥ 100	≥ 100

In presence of glycerol too, the nucleates cause a marked depression of the fluorescence of stilbamidine, but there is still a strong fluorescence remaining. In presence and in absence of nucleates, the fluorescence increases with increasing amounts of glycerol.

IV) Comparison of effects on fluorescence by reagents, added in approximately equimolar amounts:

	Fluorescence readings
1) 1 cc. stilbam. to 25 cc. H ₂ O	51.3
2) 1 cc. stilbam. + 8 cc. C ₂ H ₅ OH to 25 cc. H ₂ O	85.7
3) 1 cc. stilbam. + 5.5 cc. CH ₃ OH to 25 cc. H ₂ O	53.6
4) 1 cc. stilbam. + 10.1 cc. acetone to 25 cc. H ₂ O	90.9
5) 1 cc. stilbam. + 10 cc. glycerol to 25 cc. H ₂ O	> 100
6) 1 cc. stilbam. + 2 cc. DNA* sol. 30 mg. C ₇ to 25 cc. H ₂ O	set at 15
7) 1 cc. stilbam. + 8 cc. C ₂ H ₅ OH + 2 cc. DNA* sol. 30 mg. C ₇ to 25 cc. H ₂ O	30.7
8) 1 cc. stilbam. + 5.5 cc. CH ₃ OH + 2 cc. DNA* sol. 30 mg. C ₇ to 25 cc. H ₂ O	14.8
9) 1 cc. stilbam. + 10.1 cc. acetone + 2 cc. DNA* sol. 30 mg. C ₇ to 25 cc. H ₂ O	31.5
10) 1 cc. stilbam. + 10 cc. glycerol + 2 cc. DNA* sol. 30 mg. C ₇ to 25 cc. H ₂ O	58.2

* Deoxyribosenucleic Acid (Bios).

In both these series the fluorescence-increasing effect diminishes in the order: glycerol > acetone > ethanol > methanol ≥ stilbamidine (stilbam. plus nucl.) alone.

V) As xylene does not mix with water, a sample with 1 cc. stilbam., filled to 25 cc. with xylene (Merek), shows no fluorescence. If, however, the sample contains so much ethanol that a homogenous mixture with xylene results, the latter causes a strong increase of fluorescence over and above that of stilbamidine with ethanol alone:

	Fluorescence readings
1) 1 cc. stilbam. to 25 cc. H_2O	set at 50
2) 1 cc. stilbam. to 25 cc. xylene	0
3) 1 cc. stilbam. + 12 cc. ethanol 100% to 25 cc. in H_2O	110
4) 1 cc. stilbam. + 12 cc. ethanol 100% to 25 cc. in xylene	beyond scale

The same result as in 4) is obtained with combinations of xylene and C_2H_5OH : 5 to 19 cc. or 10 to 14 cc.

B. 2-hydroxystilbamidine

The reagents investigated above exhibit the same increasing effect on the fluorescence of 2-hydroxystilbamidine as with stilbamidine. Nucleates also increase the fluorescence of the 2-hydroxy-compound. Thus, it was to be expected that nucleates plus one of the reagents would give a summation of their effects. This was found to be the case.

2-hydroxystilbamidine diisethionate (Merek) in 10 mg. per cent aqueous sol. VI)

cm ³ ..	2-hydro- xystilb.	Na nucl.	Ethanol	Methanol	Acetone	Glycerol	Filled with	Fluorescence reading	Color of fluor.
1)	1	—	—	—	—	—	H ₂ O to 25 cm ³ .	set at 15	weakly red- dish
2)	1	—	—	10	—	—	" "	53.5	
3)	1	—	10	—	—	—	" "	96.0	brown
4)	1	—	—	—	10	—	" "	84.6	red-brown
5)	1	—	—	—	—	10	" "	55.0	pinkish white
6)	1	—	—	to 25 cc.	—	—	—	>100	yellowish
7)	1	—	—	—	—	to 25 cc.	—	beyond scale!	bluish white
8)	1	2	—	—	—	—	" "	79.8	yellow
9)	1	2	—	10	—	—	" "	>100	"
10)	1	2	—	to 25 cc.	—	—	—	≥100	green-yellow
11)	1	2	—	—	—	to 25 cc.	—	beyond scale!	yellow

VII) A comparison of the effects of the different reagents as in IV:

	Fluorescence reading
1) 1 cc. 2 OH stilb. to 25 cc. H_2O	set at 15
2) 1 cc. 2 OH stilb. + 8 cc. C_2H_5OH to 25 cc. H_2O	68.2
3) 1 cc. 2 OH stilb. + 5.5 cc. CH_3OH to 25 cc. H_2O	30.0
4) 1 cc. 2 OH stilb. + 10.1 cc. acetone to 25 cc. H_2O	87.5
5) 1 cc. 2 OH stilb. + 10 cc. glycerol to 25 cc. H_2O	55.0
6) 1 cc. 2 OH stilb. + 2 cc. DNA 30 mg. % to 25 cc. H_2O	set at 50
7) 1 cc. 2 OH stilb. + 8 cc. C_2H_5OH + 2 cc. DNA 30 mg. % to 25 cc. H_2O	93.3
8) 1 cc. 2 OH stilb. + 5.5 cc. CH_3OH + 2 cc. DNA 30 mg. % to 25 cc. H_2O	66.2
9) 1 cc. 2 OH stilb. + 10.1 cc. acetone + 2 cc. DNA 30 mg. % to 25 cc. H_2O	92.8
10) 1 cc. 2 OH stilb. + 10 cc. glycerol + 2 cc. DNA 30 mg. % to 25 cc. H_2O	79.1

In both series the increasing effects on fluorescence diminish here in the order: acetone \geq ethanol > glycerol > methanol > 2-OH stilbam. (2-OH stilbam. plus DNA) alone.

VIII) The experiment with xylene as in V gave the following result with 2-OH stilbamidine:

	Fluorescence reading
1) 1 cc. 2 OH stilb. to 25 cc. xylene.....	0
2) 1 cc. 2 OH stilb. + ethanol 12 cc. to 25 cc. H ₂ O.....	>100
3) 1 cc. 2 OH stilb. + ethanol 12 cc. to 25 cc. xylene.....	beyond scale!

Sections with 2-OH stilbamidine, when fixed with xylene, alone show no fluorescence.

SUMMARY

It is shown that addition of glycerol, ethanol, methanol, and acetone increase the fluorescence of solutions of stilbamidine and 2-hydroxystilbamidine. Addition of nucleates to these mixtures causes an additional increase in the case of 2-hydroxystilbamidine, while addition of nucleates diminishes the fluorescence of stilbamidine-glycerol and stilbamidine-alcohol mixtures. Addition of nucleates brings the fluorescence of stilbamidine-alcohol and stilbamidine-acetone mixtures down to the fluorescence of stilbamidine-nucleate solutions, while in the case of stilbamidine-glycerol mixtures a strong fluorescence still persists even after addition of nucleates.

The order of the intensity of fluorescence of stilbamidine solutions, caused by addition of the reagents mentioned, is: glycerol > acetone > ethanol > methanol. Under the same conditions the order for the fluorescence with 2-hydroxystilbamidine solutions is the following: acetone > ethanol > glycerol > methanol. Xylene, when added to either diamidine (in aqueous solution), has no effect on their fluorescence, as xylene does not mix with water. On the other hand: addition of a homogenous mixture of xylene and ethanol to diamidine solutions increases the fluorescence much more than addition of ethanol alone.

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THE INFLUENCE OF EXPERIMENTAL HYDRONEPHROSIS AND OF SEVERAL AMINO ACIDS ON THE NEPHROTOXIC ACTION OF DL-ETHIONINE*

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DL-Ethionine, the *S*-ethyl analog of methionine and a presumed methionine antagonist, produces marked tissue changes in the albino rat. It causes fatty changes in the liver predominantly of female animals (1, 2) and degenerative changes in the exocrine portion of the pancreas in both sexes (3, 4, 5). The pancreatic changes are more pronounced when animals are on a protein depletion diet (6). The third organ to be involved is the kidney. Extensive necrotic changes in the inner cortical zone are found occasionally in male animals and very rarely in female animals on a normal diet. However, these changes are quite severe and regularly observed in male animals on a protein depletion diet and somewhat less frequent in female animals on such a dietary regime following the parenteral administration of ethionine (7).

Oliver has called attention to the descriptions in the literature of acute toxic damage said to occur in all parts of the nephron (8). He pointed out, however, that the identification in histologic sections of certain portions of the nephron was difficult enough under normal circumstances and quite impossible when pathological lesions have altered their characteristic structure. All toxic lesions without associated vascular damage so far examined were found to be limited to the proximal convolutions when investigated by the dissection technique. When this technique was applied to kidneys damaged by ethionine the necrotic changes were found to be confined to the distal portions of the convoluted tubules (7). There exists, therefore, a close similarity between the renal action of a metabolic amino acid antagonist and the common renal poisons.

It seemed therefore, of interest to further elucidate the possible mechanism of the renal action of ethionine. An attempt was made to modify the nephrotoxic action of ethionine by methods which are known to influence the toxicity of several kidney damaging agents. For this reason the influence of experimental hydronephrosis was studied and in additional experiments the possible protective action of various amino acids upon the nephrotoxic action of ethionine was investigated.

METHODS

Male albino rats of the Wistar strain weighing between 150 and 250 grams were used. The animals were put on a protein depletion diet containing approximately 0.2% protein for a period of 10 to 14 days. The diet consisted of 77.6 parts of corn starch, 15 parts of hydrogenated cotton seed oil (Criseo), 4 parts of salt mixture U.S.P. XIV, 4 parts of ruffex and 0.4 parts of Brewers yeast powder (Nutritional Biochemical Corp., Cleveland, Ohio.) The animals received in addition 1 drop of cod liver oil twice weekly. For the production of experimental hydronephrosis the right ureter was ligated in light ether anesthesia in 10

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animals. Twenty-four hours later these rats were given 1 mg. dl-ethionine (α -amino- γ -ethylthiol butyric acid) (Nutritional Biochemical Corp.) per gram body weight, divided in 3 doses, intraperitoneally and sacrificed 48 hours later.

The amino acids to be tested were dissolved in distilled water, adjusted to a pH 7, 2 if necessary, and injected in amounts of 3 ml intraperitoneally 30 minutes before, simultaneously with and 30 minutes after the intramuscular administration of 1 mg ethionine per gram body weight. These animals were likewise sacrificed 48 hours later. In previous experi-

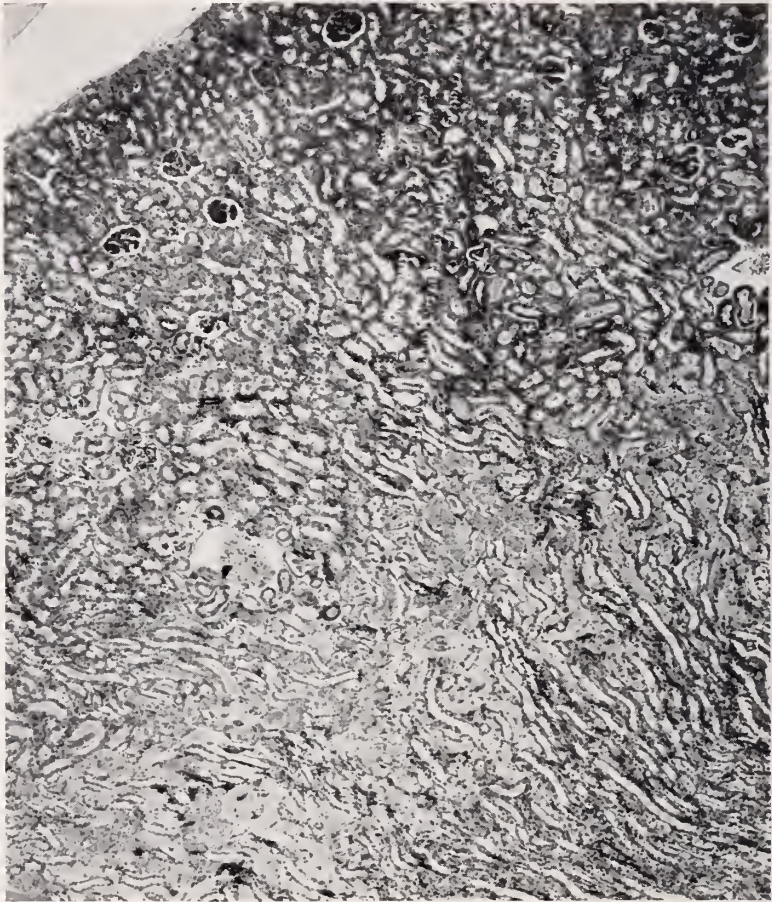


FIG. 1. Microscopic section of the left unobstructed kidney. Extensive necrosis involving the distal portion of the proximal convoluted tubules is seen. Hematoxylin eosin $\times 75$.

ments renal damage was demonstrable as early as 6 hours after the administration of the drug and reached its height 24 to 48 hours later. The degree of renal damage was expressed as 0, 1, 1+, 2+, 3+, and 4+. In kidneys considered to show \pm damage only few necrotic tubules could be seen while in those with 1+ damage occasional ones appeared necrotic

RESULTS

1. *The influence of experimental hydronephrosis.* The kidneys of all 10 animals with uninterrupted urinary flow showed renal necrosis. The damage was estimated to be 1+ in 2 instances, 2+ in one, 3+ in six and 4+ in one kidney. In all kidneys with ligated ureters

there was noticed dilatation of the renal pelvis on gross examination. Under the microscope there was dilatation of the renal tubules which extended in some instances into the proximal convolutions (See Figure 1). There was present flattening of epithelial cells and also parenchymatous and vacuolar degeneration in the cytoplasm in some of the proximal convoluted tubules. Changes of this kind may occur within short times after the ligation of the ureters (9, 10). In contrast to the contro-lateral non obstructed kidney there was almost complete

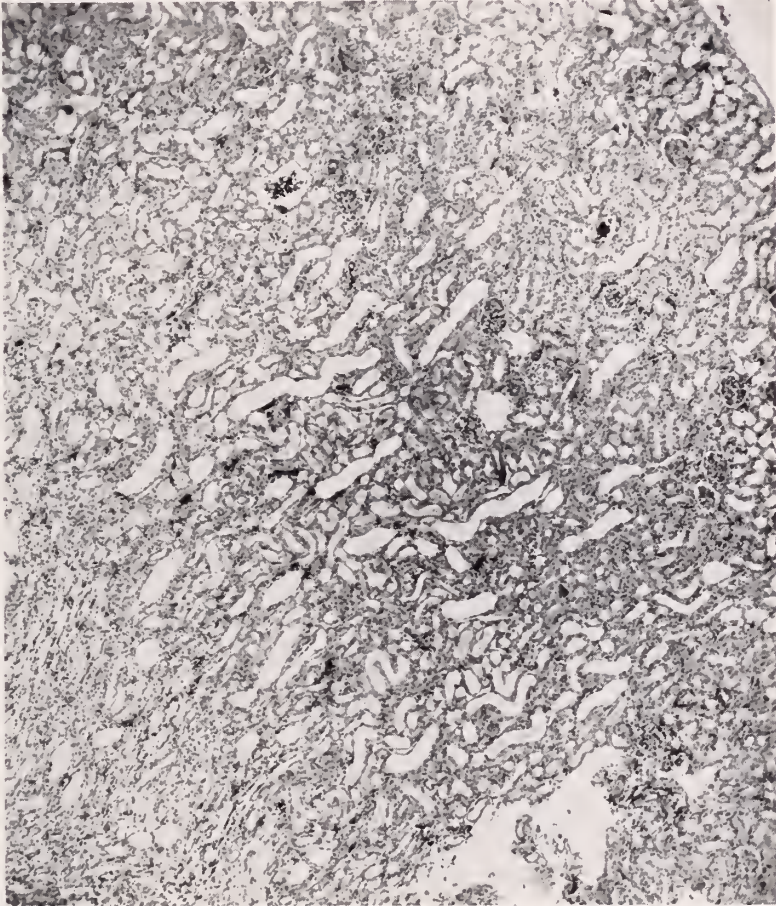


FIG. 2. Microscopic section of the right obstructed kidney of the same animal as shown in figure 1. Focal dilatation of tubules is seen to extend into the outer cortical zone. Renal necrosis is absent. Hematoxylin eosin $\times 75$.

absence of tubular necrosis. Only very occasionally and after careful search could a few necrotic tubular cells be detected.

2. *The influence of several amino acids upon the nephrotoxic action of ethionine.* The effect of one intramuscular injection of 1 mg ethionine per gram body weight on the kidney of control animals was comparable to that of the same amount given in 3 divided doses by intraperitoneal injection as previously described. Of 9 animals so injected one showed a \pm , two 2+ damage, four 3+ renal damage while the remaining two showed 4+ damage.

The amino acids tested can be seen from Table I. A considerable number of rats did not survive a period of 48 hours. Such increase in mortality under the experimental conditions

used was not encountered previously with a mercurial diuretic and dl-serine as nephrotoxic agents. Although the number of animals used in these experiments is small, the deleterious effect of several amino acids, particularly glycine, is very impressive. This aspect of the problem is presently under study.

In spite of the large amounts of the administered amino acids dl-alpha alanine, 1(+) arginine monohydrochloride, glycine and dl-threonine showed no protection. Dl-methionine was definitely beneficial although its effect was less pronounced than when it was given in 3 divided doses preceding the administration of equimolecular amounts of ethionine as previously described (7).

TABLE I

Effect of several amino acids on renal toxicity of dl-ethionine (1 mg per g body wt) on male rats on a protein depletion diet

SUBSTANCE TESTED	AMT. IN MG.	TOTAL NO. OF RATS INJECTED	DIED WITHIN 48 HOURS	SURVIVING RATS		NO. OF RATS SHOWING LESIONS					
				<i>c</i> _t	Number	0	±	1+	2+	3+	4+
-----	*	10	1	10	9	—	1	—	2	4	2
Dl-alpha-alanine.....	3 × 300	8	3	60	5	—	—	—	2	3	—
1(+) Arginine monohydrochloride.....	3 × 300	10	5	50	5	—	—	1	1	1	2
Glycine.....	3 × 300	20	17	15	3	—	—	—	1	1	1
Dl-Methionine.....	3 × 150	7	1	85	6	2	2	1	1	—	—
Dl-Threonine.....	3 × 300	9	3	40	6	—	—	—	3	2	1

* 3 × 3 ml physiological saline solution.

DISCUSSION

Morphological evidence of the deposition of administered amino acids in the cells of the proximal convoluted tubules has been brought forward by Oliver (11). When living cells were observed in physiological saline solutions or when frozen section of formalin fixed kidneys were studied by the phase microscope innumerable small droplets were seen within the cells of the proximal convoluted tubules. If stained appropriately these droplets were strongly Gram positive. They resembled closely those following the administration of protein although they were smaller in size and more numerous.

At normal plasma concentrations the reabsorption of amino acids is practically complete (12). Elevation of the plasma concentration leads to increase in the rate of tubular reabsorption. If, however, the process of reabsorption fails to keep pace with the increased rate of amino acid filtration by the glomeruli, increased amounts are excreted in the urine. If several amino acids are given competition for reabsorption may occur, e.g. glycine was found to depress the reabsorption of arginine. Competition for transport, however, has not only been reported for amino acids but also for a number of compounds unrelated by chemical structure (13).

It has been previously shown that certain amino acids are able to modify very markedly the nephrotoxic action of mercurial diuretics (14) as well as of dl-serine (15). The beneficial effect seen in microscopic section as well as the reduced proteinuria in the case of mercury was attributed to the competitive

suppression of tubular reabsorption of the injurious substances. The favorable effect of albumin upon the renal toxicity of mercurial diuretics was attributed by Lippman in a similar manner to the inhibition of mercurial reabsorption when the tubules are saturated with protein (16). Radioautographs of kidneys of rats given bovine albumin showed considerably less radio mercury localized in the renal cortex than in that of control animals. Diminished renal toxicity was therefore associated with diminished localization of radiomercury in the kidneys (17).

The amino acids tested were chosen because of their effectiveness in reducing the renal toxicity of either mercury or serine. However, no beneficial effect was seen with the exception of methionine. Methionine, however, counteracts all of the pathological tissue changes in the rat (1, 3, 7). An at least partial explanation for its action was established by the observation of Simpson, Farber and Tarver (18). These authors found that ethionine inhibits to a marked degree the incorporation of radioactively labeled methionine into the protein of the liver and kidneys of intact rats. This inhibition was completely prevented by methionine. Since all other amino acids were found ineffective it must be concluded that they are unable to block the reabsorption of significant amounts of ethionine. The other possible explanation for the failure of these amino acids to modify the nephrotoxic action of ethionine could be due to a direct action of the ethionine circulating in the blood stream upon renal tubular cells. If that were the case ethionine would exercise its damaging effect without being reabsorbed from the tubules. The protective effect of experimental hydronephrosis, however, does not favor this latter explanation.

Depression of the nephrotic action of mercury bichloride 14 to 24 hours following the ligation of a ureter was first described by Elbe (19) and later confirmed by Kosugi (9) and Wilmer (20). Experimental hydronephrosis protects likewise against uranium nitrate (20, 21) as well as against the nephrotoxic action of dl-serine (22). In contrast to the above mentioned substances sucrose (23) as well as racemic tartaric acids and diethyl glycol produced the same amount of hydropic degeneration in the cortical tubules of the hydronephrotic and the normal kidney (20). In this latter instance the toxic substances exercise their action apparently from the blood stream before being excreted through the glomerular filter. If, however, the hydronephrotic kidney is protected against a renal poison, the latter obviously can act upon the kidney only after it has passed into the glomerular filtrate and is reabsorbed by the proximal convoluted tubules.

Hydronephrosis of longer standing interferes with the process of glomerular filtration and tubular reabsorption. That functional disturbances can be demonstrated, however, very soon after experimental ligation of the ureter has been known for many years. In acute experiments with unilateral ligation of the ureter, simultaneous analysis of the urine from both kidneys shows a decreased concentration of nitrogenous constituents and electrolytes in the urine from the obstructed side as well as a considerable reduction in the excretion of injected indigo-carmin (24, 25). Whether these changes are due predominantly

to interferences with glomerular filtration or disturbed tubular function or to a combination of both factors is not known. Active glomerular filtration continues for some time in experimental hydronephrosis (26). However, a study of renal circulation with the use of cineangiography shows a considerable decrease in the amount of circulating blood as soon as 24 hours after experimental urethral ligation (27). This decrease in blood supply probably depresses glomerular filtration to a considerable degree. Histochemical evidence for functional disturbances in the renal tubules was first described by Willmer who noticed marked decrease in alkaline phosphatase activity (28). The first evidence, however, of such decrease is not seen before 36 hours have elapsed (22).

The results of the experiments with hydronephrosis seem to indicate that ethionine acts in a similar manner as do the common renal poisons, that is not directly from the blood stream but only after it has been filtered through the glomerular membrane and has been reabsorbed by the proximal convoluted tubules.

SUMMARY

The acute necrosis within the distal portion of the proximal convoluted tubules regularly seen in male rats on a protein deficient diet caused by dl-ethionine is not favorably influenced by several amino acids which are known to have a beneficial effect upon renal damage caused by a mercurial diuretic or dl-serine. In contrast experimental hydronephrosis protects the kidney against the nephrotoxic action of dl-ethionine. It is concluded that dl-ethionine acts upon the renal tubules after having been filtered through the glomeruli and having been reabsorbed by the proximal convoluted tubules. The amino acids tested are not able to suppress the reabsorption of the injurious substance to a sufficient degree.

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UPTAKE OF P^{32} IN SEMINAL VESICLES OF CASTRATE RATS AFTER TREATMENT WITH TESTOSTERONE PROPIONATE*

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Growth of the accessory sex organs of rodents is controlled mainly by the internal secretion of the gonads (1, 2). Measurement of the weight increase of the seminal vesicles of the castrate rat following injection of androgen has been shown to be a reliable procedure for the bio-assay of androgens (3, 4). Voss and Loewe (5) were the first to suggest hyperplasia and mitotic activity in the seminal vesicles of the castrate mouse as a possible index for testicular hormone activity. Using the colchicine technique, numerous mitotic figures could be demonstrated by us (6, 7, 8) in the seminal vesicles of castrate mice and rats after injection of androgens. Other investigators (9, 10, 11, 12, 13) have reported similar observations. The abundance of mitotic figures in the growing seminal vesicles is in striking contrast to their absence in the resting seminal vesicles of the castrate rat or mouse.

Since the seminal vesicles of castrate rats increase rapidly in size and in mitotic activity after injection of androgen, this phenomenon forms a possible means of studying the regeneration of nucleoprotein during the process of growth. As a first step in doing this, we have attempted to survey the various changes in nucleoproteins by comparing the radioactivity of certain chemical fractions of growing and resting seminal vesicles after giving phosphate labeled with P^{32} to castrated rats.

MATERIALS AND METHODS

Male Wistar rats were castrated when 29 to 32 days old. Experiments were started 7 to 35 days after castration. It has been shown by Hays and Mathieson (3) that the seminal vesicles of rats castrated when 30 to 33 days old exhibit the same increase in weight whether the animals are injected with testosterone propionate as early as 7 or as late as 350 days after castration. In our experiments one group of rats was injected subcutaneously with a single dose of 2.5 mg. of testosterone propionate dissolved in sesame oil (TP). Another group of castrated rats of the same age was left untreated (Controls).

Carrier free P^{32} in the chemical form of H_3PO_4 , as received from Oak Ridge, was diluted

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with water so that the dose to be given contained 50 microcurie in 0.2 to 0.6 ml. This solution was administered subcutaneously 72 hours after injection of TP. The controls received P^{32} only. All animals were killed with ether five hours after administration of P^{32} .

In the first series of experiments the seminal vesicles were removed immediately after death, weighed, digested with 10 per cent KOH, dried, and the activity of each counted on planchets. Both a thin-window Geiger-Muller counter and a windowless flow-gas proportional counter were used.

In the second series the seminal vesicles were removed in the same way. Batches of seminal vesicles weighing from two hundred to four hundred mg. were pooled, frozen, and ground up. This tissue was then fractionated according to the method of Schmidt and Thannhauser (14) as modified by Friedkin and Lehninger (15). The activity of aliquots of the fractions containing inorganic P, ribosenucleic acid (RNA), and desoxy-ribosenucleic

TABLE I

Uptake of P^{32} by seminal vesicles of treated (TP) and control rats

TREATMENT	NO. OF RATS	WEIGHT OF S.V. (MG.)	P^{32} C/SEC./100 MG.	INSTRUMENT USED
TP	13	49.8 \pm 3.0 ^x	124.3 \pm 13.4 ^x	G. M. counter
Controls	9	14.0 \pm 0.6 ^x	33.7 \pm 6.6 ^x	G. M. counter
TP	6	49.8 \pm 1.4 ^x	896 \pm 160 ^x	Flow-gas counter
Controls	7	9.6 \pm 1.3 ^x	279 \pm 24 ^x	Flow-gas counter

x—Standard error of the mean.

TABLE II

P^{31} and P^{32} content of seminal vesicles

TREATMENT	WEIGHT OF TISSUE (MG.)	INORGANIC		RNA		DNA		SPECIFIC ACTIVITY		
		P^{32}	P^{31}	P^{32}	P^{31}	P^{32}	P^{31}	Inorg.	RNA	DNA
TP	354	543	37.6	118.7	48.8	29.9	33.6	14.5	2.4	0.9
TP	372	589	40.2	115.7	49.0	30.7	34.6	14.7	2.4	0.9
TP	416	526	39.8	107.3	50.8	28.7	34.5	13.2	2.1	0.8
Control	211	167	33.3	19.7	22.5	0.31	67.1	5.0	0.9	0.005
Control	213	188	33.9	21.0	22.0	0.56	61.7	5.5	1.0	0.009

P^{31} = μ g. per 100 mg. fresh tissue. P^{32} = counts per second per 100 mg. fresh tissue. Specific activity P^{32}/P^{31} .

acid (DNA) was measured with the same instruments as in the first series. Stable phosphorus (P^{31}) was determined colorimetrically by the method of Gomori (16).

In the present paper the terms RNA P and DNA P refer to the phosphorus content of the tissue fractions as obtained by the method of Schmidt and Thannhauser.

RESULTS

The results of the first series of experiments are shown in Table I. These data show clearly that there is a significant rise in P^{32} uptake in the seminal vesicles treated with TP.

The results of a fractionation experiment are recorded in Table II. Three batches of 7 TP seminal vesicles each and two batches of 19 control seminal vesicles each were prepared according to the method of Friedkin and Lehninger.

Counts of the fractions containing inorganic P, RNA P, and DNA P were made with the flow-gas counter. Specific activity is expressed for a given mass of tissue as the ratio of counts per second to mg. of total phosphorus.

DISCUSSION

Growing tissue accumulates more P^{32} than fully grown tissue. This is explained by Hevesy (17) with the formation of labeled phosphorus compounds in growing tissue. Kolman and Rusch (18) administered phosphate labeled with P^{32} to rats and mice and compared the P^{32} content of nucleoproteins of normal liver and of liver in which cancer was produced by feeding azo dyes. The tumorous liver, in which a rapid formation of new cells takes place, was found to have a 45 per cent increase in accumulation of P^{32} , compared with the normal liver. A similar difference has been shown for several examples of growth induced in target tissues by hormones. The uptake of P^{32} by the uterus of the immature rat is enhanced by the administration of estradiol. P^{32} is used to form compounds containing P^{32} in the uterus primed by estradiol as evidenced by the increase

TABLE III
Ratio of specific activity of RNA P to that of DNA P after administration of P^{32} to rats

ORGAN	TIME AFTER ADMINISTRA- TION OF P^{32} (HOURS)	RNA P DNA P	AUTHOR
Liver.....	2	33:1	Hammarsten and Hevesy
Spleen.....	2	3:1	Hammarsten and Hevesy
Intestinal mucosa.....	2	2:1	Hammarsten and Hevesy
Castrate seminal vesicle TP.....	5	3:1	Fleischmann and Fleischmann
Castrate seminal vesicle Control.....	5	136:1	Fleischmann and Fleischmann
Jensen sarcoma.....	2½	2:1	Holmes

of P^{32} in the tissue fraction insoluble in acid (19). The growth of the crop-sac of the pigeon induced by prolactin is associated with an increased concentration of P^{31} and administered P^{32} . Fractionation of the tissue gave results which suggest that inorganic phosphorus enters the cells of the stimulated gland at an increased rate and serves as the source of phosphate for the synthesis of organic phosphorus compounds, presumably nucleoproteins (20). Treatment with thyroid stimulating hormone increases the amount of P^{32} accumulated by the thyroid gland of the guinea pig (21). The results of our study on seminal vesicles primed by testosterone propionate are in good agreement with these reports on the enhanced uptake of P^{32} by growing tissues.

Caspersson (22) has recently reviewed the evidence for the association of DNA synthesis and mitosis. In view of Caspersson's work the great increase in the radio-activity of DNA P due to treatment with testosterone propionate is of interest. The effect on the radio-activity of RNA P is much smaller. The ratio of specific activity of RNA P to that of DNA P in tissues of rats after administration of P^{32} is represented in Table III. In addition to our data on seminal vesicles, the results of Hammarsten and Hevesy (23) on some other normal tis-

sues and of Holmes (24) on a Jensen sarcoma of the rat are also recorded. These figures are only roughly comparable to ours as Hammarsten and Hevesy used a slightly different method of fractionation. Moreover, the period of exposure to P^{32} is not the same in the various experiments compared in Table III. However, the assumption can be made that the ratio of specific activity is of the same order of magnitude in experiments lasting a few hours. The data in Table III suggest that great mitotic activity is associated with a low (2:1 or 3:1) ratio of the specific activity of RNA P to that of DNA P. The spleen, the intestinal mucosa, the seminal vesicle treated with TP, and the Jensen sarcoma are tissues with great mitotic activity. The ratio of 33:1 found in the liver is suggestive of the low mitotic activity of this organ. The high ratio (136:1) found in the untreated seminal vesicle may be associated with the absence of mitotic activity of this resting tissue.

The experiments indicate that the rapid growth of the seminal vesicles of castrate rats under the influence of testosterone is associated with greater incorporation of P^{32} from inorganic phosphate in the phosphorus of the desoxyribonucleic acid fraction than in that of the ribonucleic acid fraction, as obtained by the method of Schmidt and Thannhauser.

SUMMARY

1. Treatment with testosterone propionate increases the amount of P^{32} accumulated by the seminal vesicles of the castrated rat.
2. Treatment with testosterone propionate increases the amount of P^{32} in the seminal vesicles accumulated in the desoxyribonucleic acid fraction, as prepared by the method of Schmidt and Thannhauser.
3. The relationship of formation of nucleic acids to mitotic activity in the seminal vesicles is discussed.

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THE INTEGRATED ROLE OF CATECHOLAMINES, MINERALOCORTICOIDS AND SODIUM IN HYPER- AND HYPOTENSION*

(A WORKING HYPOTHESIS)

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The cardiovascular situation (diastolic hypertension) is practically identical in three otherwise heterogeneous syndromes, namely (a) pheochromocytoma (sustained hypertension type), (b) hyperadrenocorticism (Cushing's syndrome) and (c) essential hypertension. This suggests the probable existence of a common pathogenic denominator. The two first named forms of hypertension are curable by removal of a catecholamine-producing pheochromocytoma or of a mineralocorticoid-producing adrenal cortical tumor respectively. Essential hypertension can be ameliorated or cured by (a) sympathectomy, (b) adrenalectomy, and (c) sodium withdrawal. Each of these methods attacks the fundamental mechanism of hypertension at a different point: (a) Sympathectomy is in essence equivalent to the removal of a pheochromocytoma in that it reduces the amount of catecholamine-producing tissue; (b) Adrenalectomy is equivalent to removal of an adrenal cortical tumor in that it eliminates the mineralocorticoid-producing tissue; (c) Sodium withdrawal is comparable to adrenalectomy in that it deprives the body of the material by means of which the mineralocorticoids exert their most characteristic effects on the cardiovascular system.

It is known that the blood pressure-raising action of DCA (a presumable representative of the natural mineralocorticoids) is intensified by the ingestion of sodium (1, 2, 3, 4, 5, 6) and weakened or abolished by sodium withdrawal (1, 7, 8, 9, 10). This, as well as the favorable response of hypertensive patients who show signs of adrenal cortical over-function (11, 12) to a sodium-poor diet, and the hypotension of sodium-depleted hypoadrenocortical patients, indicates that the sodium ion is basically involved in the hypertensive and hypotensive effects respectively of mineralocorticoid over- and under-activity.

The most important feature of DCA action consists of its unique ability to increase the intracellular concentration of sodium (13, 14, 15, 16, 17, 18, 19) and thus to affect the intra-extracellular electrolyte gradient. The latter has been shown to influence the electric cell membrane potential which in turn determines the contraction amplitude of the individual muscle cell under adequate stimulation, in proportion to the magnitude of the intra-extracellular electrolyte concentration difference (20, 21). It appears conceivable, therefore, that DCA, by depositing sodium in the cells of the cardiovascular system, would increase their power of contraction, whereas cellular sodium depletion, caused either by mineralocorticoid deficiency or by dietary sodium withdrawal, would weaken their contractile responsiveness to adequate stimuli.

* The personal investigations (32, 41) upon which this article is largely based were aided by a grant of the United States Public Health Service (National Heart Institute).

As far as the latter are concerned, it is known that the sympathogenic catecholamines (epinephrine and nor-epinephrine) act as depolarizing agents (22, 23, 24) and that the cardiovascular contractile cells are constantly exposed to an influx of pressor catecholamines, either by way of direct neurosecretion from the postganglionic sympathetic fibers (25, 26) (prevailingly nor-epinephrine (27, 28, 29)) or via the blood stream from the adrenal medulla (prevailingly epinephrine (27, 30)).

The pressor effectiveness of epinephrine and nor-epinephrine is modified by changes of mineralocorticoid action and of sodium distribution in the following respects: (a) potentiation of the pressor effects by pre-treatment with DCA (1, 31, 32, 33); (b) weakening of the pressor effects in states of adrenal cortical insufficiency (34, 35, 36, 37, 38, 39, 40); (c) weakening or abolition of the pressor effects during sodium withdrawal (41); (d) no potentiation of the pressor effects by DCA during sodium withdrawal (41) (Fig. 1).

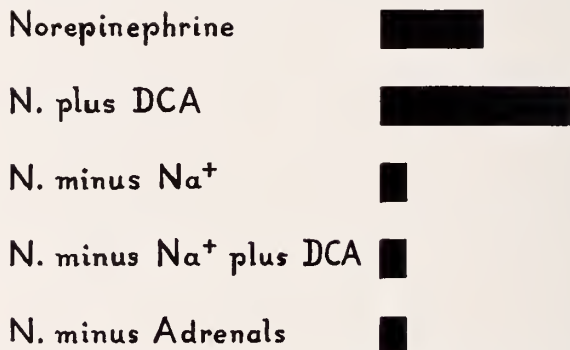


FIG. 1. The black squares indicate approximately the magnitude of the pressor effects of a given dose of infused nor-epinephrine under various modifying influences.

These observations suggest that the amount of sodium within the cardiovascular contractile cells determines the pressor effectiveness of the sympathogenic catecholamines and that this pressor effectiveness is regulated by the sodium-depositing activity of the mineralocorticoids.

Thus, the blood pressure level appears to be influenced by the integrated interaction of (a) the quantity of catecholamines (prevailingly nor-epinephrine) (29, 42) in the vascular walls and the heart muscle (27, 28, 43); (b) the quantity of sodium within the cardiovascular cells (intra-extracellular electrolyte concentration gradient); (c) the quantity of sodium-depositing mineralocorticoids as regulators of "(b)" and thereby of the effects exerted by "(a)".

As depicted in Fig. 2, the role of excess amounts of adrenal catecholamines and mineralocorticoids respectively, causing hypertension in cases of pheochromocytoma and of adrenal cortical tumors, is fairly obvious. In essential hypertension, on the other hand, the situation appears more problematic and open to speculation. It can be said, however, that some findings are available which indirectly indicate a sympathetic neurosecretory (notably nor-epinephrine) as well as adrenocortical over-activity in certain types of essential hypertension:

An exaggerated nor-epinephrine action in essential hypertension is suggested

(a) by the general vasoconstrictor effect of this neurohormone which produces diastolic blood pressure elevations like those characteristic of essential hypertension (32, 44, 45, 46); (b) by the demonstrable existence of various neurogenic (neurosecretory) mechanisms involved in the pathogenesis of essential hyper-

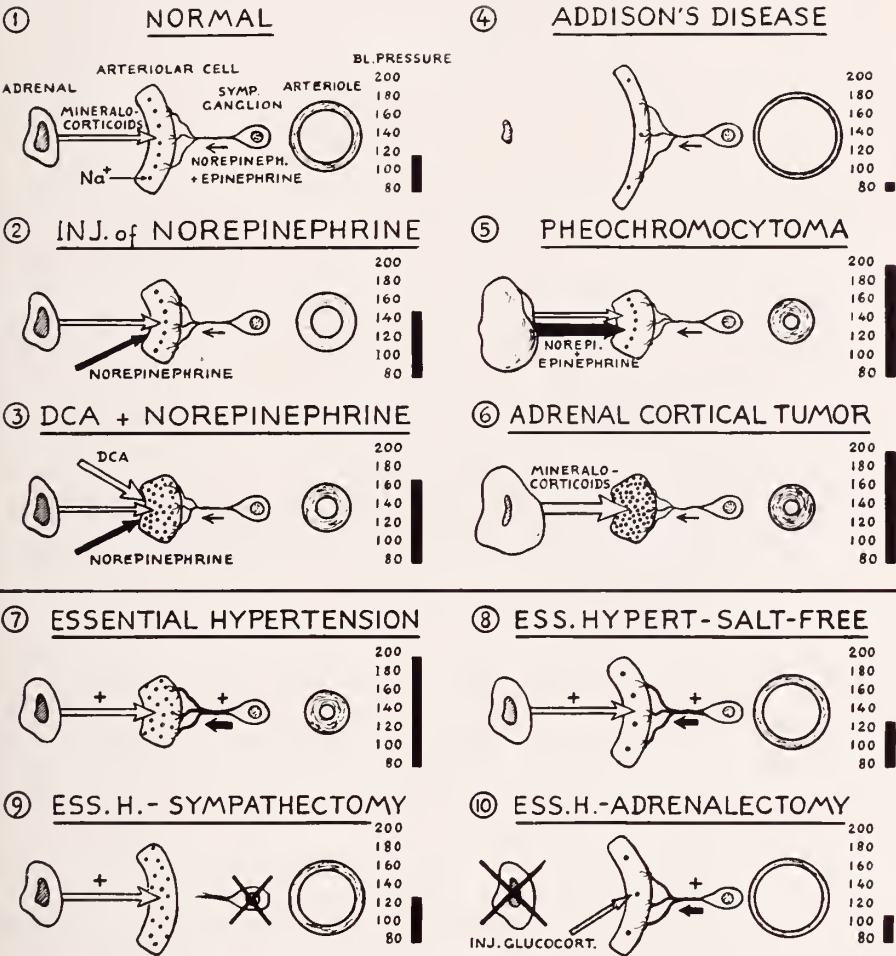


FIG. 2. Schematic representation of the vasoconstrictor and pressor effects of (a) catecholamines (nor-epinephrine and epinephrine) (secreted by sympathetic fibers or by the adrenal medulla or injected); (b) mineralocorticoids (DCA) (secreted by the adrenal cortex or injected); (c) intracellular sodium (black dots) (maintained or increased by mineralocorticoids; decreased by lack of mineralocorticoids or by salt withdrawal).

tension (literature, see 47); (c) by the therapeutic successes of sympathectomy (48, 49, 50) and of ganglionic blocking (51) and sympatholytic (52, 53) agents.

An exaggerated mineralocorticoid activity is suggested (a) by a diminished sodium excretion with thermal sweat in at least part of the cases (12, 54), (b) by an increased lipid content of the adrenal cortex in essential hypertension (55, 56, 57), (c) by the therapeutic successes of adrenalectomy (58, 59) and (d) by the increased sodium concentration in the arterial walls of hypertensive

individuals (65). An increased sodium content of the tissues was also observed in hypertensive animals (70).

The sodium-retaining and pressor effectiveness of DCA and of the natural mineralocorticoids seems to depend in part on their equilibrium with the antagonistic glucocorticoids (60, 61) and may rise without actual over-production through a relative deficiency of the latter.

Apart from the sympathogenic pressor catecholamines, one has to reckon with the possible participation of other, chemically not yet clearly defined, pressor substances (VEM, pherentasin, etc.) in the mechanism of essential hypertension.

E. P. Pick (62) succeeded in 1935 in producing temporary hypertension in dogs by transfusing the blood from other dogs with neurogenic hypertension, and furthermore in abolishing neurogenic hypertension by the infusion of blood from dogs with denervated kidneys. These phenomena which would deserve further study seem to suggest the existence of a variety of still unexplored humoral mechanisms. Hence, the writer does not propose to explain all features of blood pressure regulation on the basis of the above-outlined neurohormonal-hormonal mechanism, but he believes that this mechanism occupies a key position in the normal and pathological regulation of blood pressure. It had been anticipated in 1941 by R. F. Loeb (63) and W. W. Swingle (64), who postulated an important role of the local action of electrolytes in the maintenance of vascular tone. An analogous view was recently expressed by Floyer (66). Hajdu and Szent Györgyi (71) believe that DCA influences cardiac muscular contractility "by altering the intracellular ionic atmosphere."

SUMMARY

A survey of existing clinical and experimental observations, including those of the writer and his co-workers, suggests the following hypothesis concerning the integrated action of sympathogenic catecholamines and adrenal mineralocorticoids (with sodium as the physico-chemical mediator) in the neurohormonal-hormonal system of blood pressure regulation:

The intrinsic catecholamines (especially neurogenic nor-epinephrine) act on the contractile vascular cells as depolarizing agents and serve as physiological stimuli in the maintenance of vascular tone. Their pressor effectiveness depends on the electrical membrane potential of the contractile cells which in turn is determined by the intra-extracellular electrolyte concentration difference which in turn is influenced by the adrenal mineralocorticoids, by virtue of their specific ability to deposit sodium intracellularly. Hypertension results from excess catecholamines (e.g., pheochromocytoma, "neurogenic" hypertension) or mineralocorticoids (Cushing's syndrome, "hormonal" hypertension), or both combined, provided that sufficient sodium is available in the body. Hypotension results from lack of catecholamines (e.g., sympathectomy, ganglionic blockade) or lack of mineralocorticoids (adrenalectomy, Addison's disease) or lack of extrinsic sodium (salt-poor diet) or combinations of these.

Practical application of these principles proved therapeutically effective in essential hypertension.

TABLE I

TYPE OF HYPERTENSION	POTENTIAL PATHOGENIC FACTORS	PRESUMABLE ORIGIN OF HYPERTENSION	PRESSURE-LOWERING MECHANISM OF THERAPY
Pheochromocytoma (Sustained hypert.)	Catecholamines	Increased	Decreased (Excision of tumor)
	Mineralocorticoids	—	—
	Sodium (in cells)	—	—
Cushing's syndrome	Catecholamines	—	—
	Mineralocorticoids	Increased	Decreased (Excision of tumor)
	Sodium (in cells)	Increased*	Decreased* (Excision of tumor or sodium-poor diet)
Essential hypertension	Catecholamines	Increased?	Decreased (Sympathectomy)
	Mineralocorticoids	Increased?	Decreased (Adrenalectomy)
	Sodium (in cells)	Increased?	Decreased* (Adrenalectomy or sodium-poor diet)

* Conjectural—Concluded from the intracellularly sodium-accumulating effect of injected DCA and intracellular sodium loss resulting from adrenalectomy.

ADDENDUM

Recently published observations concerning the occurrence of hypertension in nephrectomized dogs (kept alive by means of peritoneal lavage) despite additional adrenalectomy (67), and the persistence of hypertensive blood pressure levels until the onset of "more severe adrenal cortical insufficiency" (67), seem to indicate that corticoids, otherwise excreted with the urine, were retained because of the absence of both kidneys, thus delaying the hypotensive effect of true adrenal cortical hormone deficiency. Intensification of the pressor action of DCA by potassium feeding (68) and the depressor effect of potassium withdrawal (but not of combined potassium and sodium withdrawal) (69) suggest that vascular contractile power does not depend on intracellular sodium alterations alone but on more complicated features of electrolyte balance (total intra-extracellular electrolyte gradient?) under alimentary and hormonal influence.

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PHYSIOLOGIC AND PATHOLOGIC ALLERGY

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It is a great honor to be permitted to contribute to the anniversary volume dedicated to Prof. E. P. Pick, and in the following I shall discuss the difficulties arising out of the existing confusion of the terms *allergy* and *anaphylaxis*.

I propose to divide allergy into two forms: *physiologic* allergy and *pathologic* allergy. The first form represents an almost perfect and hence a most useful defense mechanism of nature against invading pathogenic microorganisms. The second, the pathologic form, is produced by foreign protein and is characterized by *hyperergic* reactions (hypersensitivity). These reactions are frequently called anaphylactic. They are not only more intensive but may be dangerous and even fatal.

Allergy, as Pirquet defined it, is simply what the word means: *altered reactivity*. This reactivity is provoked by a pathogenic substance (pathogenic microorganism, foreign protein or chemical substance) if reintroduced into the organism. The first invasion or injection is followed by an incubation period of some duration. The altered reactivity clinically manifests itself by two symptoms: the incubation time is either abolished (immediate reaction) or shortened (accelerated reaction). The change in the duration of the incubation time gave the clue for the discovery of allergy.

Some infectious diseases like diphtheria and tetanus are due to a primarily toxic Exotoxin, which must reach a certain amount before clinical symptoms are elicited. The time needed for this to occur is the incubation time. The exotoxin stimulates the production of antitoxic antibodies. These antibodies prevent further damage by the pathogenic germ neutralizing the exotoxin.

Many other infectious diseases are due to an endotoxin, a toxin inside the pathogenic germ. This means that the invading germ multiplies at first without producing symptoms and without interference by the invaded organism. Meanwhile various antibodies (bacterocidal, bacteriostatic or bacteriolytic) are formed which are capable of attacking, dissolving and killing the invader, thereby setting free the endotoxin. The endotoxin elicits the clinical symptoms of the disease. The formation of antibodies requires some time (8-14 days). This is the incubation period. The action of the antibodies is essential for terminating the unlimited multiplication of the invading germ. The destruction of the germs liberates the endotoxin. The disease caused by the endotoxin is the penalty paid to rid the system of the invader. The antibodies remain within the circulation for some time. Even after they have finally disappeared, the cells of the organism are capable of reproducing the specific antibodies more rapidly than at first (within 4-6 days). Therefore, in case of reinfection with the same germ, the antibodies can act either immediately or at least more quickly than they did at first and can more rapidly stop the multiplication of the invading germ. Almost no or, at least, much less endotoxin is set free. The clinical symptoms may not be detectable or may be very mild and so insignificant that the individual appears to

be completely immune. The immunity rests therefore upon the altered reactivity i.e. allergy of the organism brought about through the first infection. Immediate and accelerated reactivity are distinctive features of the existing allergy. Thus allergy is an excellent mechanism of defense, a physiologic response to the re-invasive pathogenic microorganism.

Our basic study of allergy was carried out with a dead substance (horse-serum). This was very advantageous because we were able to show that this dead substance, which cannot multiply, had no endotoxin, is as such not toxic, and leads to a disease only after elapse of an incubation time (8-10 days). When serum is reinjected a similar defense is established as in the case of an infectious disease. The incubation time is either abolished or shortened. Therefore, an immediate or an accelerated reaction is observed as an expression of allergy. Here too antibodies are formed. These antibodies have to break down the foreign protein. Through interaction between foreign protein and antibodies toxic substances are formed which are responsible for the clinical symptoms of serum disease. Differing from the situation in infectious diseases, *the immediate and accelerated reactivity* offer no advantage to the individual as there is no microorganism which has to be stopped from multiplication and killed. The natural defense mechanism was established to fight off the ever present danger of invasion of pathogenic germs and not for the purpose of combatting the unnatural injection of foreign protein by a physician.

The serum sickness taught us still another lesson. The immediate and accelerated reactions were characterized by greater intensity of the symptoms, sometimes quite out of proportion to the amount of serum reinjected. We reported on page 88 of our monograph the observations of a child who almost died in shock after reinjection of serum. We suspected that the serum was injected into a vein and warned therefore not to reinject serum intravenously. This hypersensitiveness, called by Pirquet hyperergic reaction, is sometimes a dangerous pathologic form of allergy. Similar hypersensitivity was already known before the publication of our observations; horses immunized by repeated injections of diphtheria or tetanus toxin died suddenly after reinjection of toxin in spite of the fact that a great amount of antitoxin was present in the serum.

About the same time as we published our studies of serum sickness, Richet and Poitiers reported their most interesting studies about hypersensitivity of dogs and other animals to the reinjection of a very small amount of Actinia venom. Already the first injection produced a toxic effect, but by reducing the dose the animal survived but was killed by reinjection of a minute amount of the venom.

Already the first injection produced a toxic effect, but by reducing the dose the animal survived but was killed by reinjection of a minute amount of the venom.

Richet coined for this phenomenon the term *Ana-phylaxis*. The name was selected to distinguish this phenomenon from a *Pro-phylactic* effect. Anaphylaxis meant the removal of a protective substance. Hyperergic reaction and anaphylaxis indicate the same phenomenon; they are a pathologic form of allergy.

Hypersensitivity exists as a pathologic form of allergy in infectious diseases too. But as a rule it plays no significant role in the symptomatology of infectious

diseases, because the immediate or accelerated action of the antibodies liberates only a very small amount of toxic substances. In bacterial allergic bronchitis and bacterial asthma it causes some difficulties. In experimentation the pathologic allergy can be demonstrated by a reinjection of a large amount of bacteria or their toxin (for instance by injection of a larger amount of tuberculin or tubercle bacilli into a tubercular guinea pig). Actually, in diseases of human beings it rarely happens that a violent hyperergic reaction develops through a massive invasion of tubercle bacilli into a tuberculous individual.

The further study of allergy showed the importance of protein substances as causative agents for a great variety of diseases characterized by hypersensitivity. These protein substances are present in pollen, house dust, animal emanations, foodstuffs, etc. Many drugs combine with the protein of the human organism creating offending proteins (*Hapten*). Asthma, hay fever, hives, eczema and other rashes are manifestations of hypersensitivity. These diseases are wrongly called allergic diseases. They are conditions in which allergy plays a great role but allergy is not a disease *per se*. Lately several diseases like Periarthritis Nodosa, Lupus Erythematosus, certain features of the rheumatic process, and nephritis show anatomical findings pathognomonic for hyperergic reaction. All these are manifestations of a pathologic form of allergy. Unfortunately, this pathologic allergy brings misery to millions of otherwise healthy individuals. No immunity exists against these substances, if hypersensitivity has once developed, just as no immunity exists against foreign serum. In the aforementioned conditions one must be satisfied either with the hope of spontaneous improvement in the tolerance or with the lowering of hypersensitivity affected by repeated injections of the offending substances (desensitisation). Of course, by avoiding when possible the contact with, or inhalation or eating of the offending substances, the individual may be free from symptoms.

SUMMARY

There are two forms of allergy. One is a physiologic and a beneficial one making it possible to fight diseases due to the invasion of pathogenic microorganisms and leading to immunity. Foreign protein is fought with a similar defense mechanism, but the allergic reaction to it is accompanied by a pathologic hypersensitivity which is frequently harmful and may be even dangerous to life. This form of allergy should be called pathologic allergy. It must be understood and taught that physiologic allergy is not a disease but a physiologic defense mechanism instituted as a protection against infectious diseases.

Therefore, the normal, useful, physiologic allergy should not be confused with the pathologic form of allergy. The anaphylactic shock and death in anaphylactic shock are only the most intensive effects of the pathologic form of allergy. To stress the pathologic allergy can only lead to a wrong conception of allergy. The beneficial and life-saving effect of the physiologic allergy outweighs by far the disadvantages of the pathologic allergy seen in diseases due to foreign protein. The term Anaphylaxis can be replaced by the term: Pathologic Allergy.

THE RELATIONSHIP OF XANTHOMA JUVENILE TO SYSTEMIC RETICULOENDOTHELIOSIS*

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Xanthomatosis of the skin in infants and children may be accompanied by high or normal cholesterol blood levels. In xanthoma tuberosum or planum (essential hypercholesteremic familial xanthomatosis) and in the secondary eruptive forms of xanthomatosis (due to idiopathic familial hyperlipemia, nephrosis, diabetes mellitus, hypothyroidism, van Gierke's disease) the cholesterol blood levels are considerably increased. In xanthoma disseminatum restricted to the skin, or accompanied or followed by systemic reticuloendotheliosis of the visceral organs (essential normocholesteremic type of xanthomatosis), e.g., Letterer-Siwe's disease, Hand-Schuller-Christian's disease, generalized lipogranulomatosis with involvement of skeleton, lymph glands, lungs and other organs, and eosinophilic granuloma of the bone—the blood cholesterol levels are normal.

This division of xanthomatosis into hypercholesteremic and normocholesteremic types was suggested on the basis of their chemical investigations by Thannhauser and Magendantz (1) in 1938 and has since been generally accepted. One of the rare exceptions to this classification is the case of van Crefeld and ter Poorten (2) where, in an infant suffering from xanthoma disseminatum of the skin and generalized visceral reticuloendotheliosis, a cholesterol blood content of 596 mg. per cent was found. This single case would not seem to justify the statement of Claireau and Lewis (3) that the division of xanthomatosis into normocholesteremic and hypercholesteremic types is unwarranted.

Xanthoma juvenile is the childhood form of xanthoma disseminatum. There is a normal blood cholesterol level and characteristic discrete, papular skin lesions. In cases where, at the same time or later on, visceral reticuloendotheliosis is seen, the skin lesions usually appear in clusters, lines, or sheets. The lesions consist of wart-like papules ranging in size from a pinhead to an almond, situated on the face, scalp, neck, limbs and trunk and frequently on the buttocks. The color of the lesions varies from golden yellow to brownish red or orange. The diagnosis of xanthomatosis should be confirmed by biopsy.

The following histological changes can be seen: There is first a petechia-like lesion around a blood vessel which may lead to extensive hemorrhage and necrosis of the epidermis covering this small area and which may disappear or develop into xanthomatosis. In these lesions, reticulum cells, sometimes a few eosinophilic cells, groups of xanthoma cells (foam cells) and spindle-shaped fibroblasts, chiefly situated in the papillary portion of the cutis are seen. This cell proliferation may be widespread either in relatively small foci or in broad sheets in the papillary portion of the cutis and penetrating the papillae (4). Foam cells and fibroblasts are predominant in the late stages of the condition. Xanthomatous

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development usually occurs earlier in the disseminated skin lesion than in visceral pathology and is quite extensive.

These changes are found in the cases of juvenile xanthoma with a benign course as well as in those patients who develop visceral pathology. The histological process in the skin lesions is basically the same as in other organs involved by reticuloendotheliosis. This fact was first stressed by Rowland (5) in his pioneer histological work on reticuloendotheliosis. In contrast to the histological findings in xanthoma tuberosum, usually no "Touton" giant cells are found. Chemically, the cholesterol content of these lesions may be 10 to 20 times that of normal skin (6).

The course of xanthoma juvenile is usually very protracted. There is no itching. After some time, some of the lesions may disappear and new ones are seen in different areas. Detailed descriptions of this condition are found in the articles of McDonagh (7), Wise (8), Jacobi and Grund (9), Wheeler (10), Sencar and Caro (11), and many others. The children showing this type of condition appear healthy and develop and grow normally. Thumhauser (12) therefore expresses the opinion that the infantile skin xanthoma of the normocholesteremic disseminated variety has a benign course and that it may disappear completely in later life. On the other hand, this author stresses the fact that there are no complete follow-up reports which would confirm his opinion. In a recent general review on xanthomatosis, Crocker (13) goes a step further and makes the optimistic statement that "There is no reason to believe that the prognosis of xanthoma disseminatum is other than excellent." He bases this prognosis on the fact that in the cases in his study there was a tendency toward slow spontaneous disappearance of the lesions, and that visceral involvement did not appear subsequently if it was not present at the time of the initial work-up. He adds that only when the lesions are numerous and are forming reddish papules, or a flat golden brown macular configuration, that the patients are suspect of possible involvement of internal organs. In these cases he recommends x-rays of chest and skeleton and a more careful follow-up.

Wile and Curtis (14) present a case where a disseminated xanthomatous skin eruption was seen in an eight months old infant who, at the age of three years, developed multiple eosinophilic granulomas of the bone that responded well to x-ray treatment. Most interesting are the cases of Schafer (15) where skin lesions were seen at birth in three infants who later developed Letterer-Siwe's rapid, fatal type of reticuloendotheliosis. Other cases which later developed visceral involvement were reported by Lamb and Lain (16), Pasey and Johnston (17), Spillman and Watrin (18), Turner, Davidson and White (19). These authors observed xanthoma disseminatum, complicated by diabetes insipidus (brain involvement) and a peculiar type of lung fibrosis. In the cases of Horsfall and Smith (20), and Lane and Smith (21), petechia-like lesions were noted which, however, histologically could be recognized as xanthomatosis and, later on, visceral involvement developed.

ILLUSTRATIVE CASES

Six pertinent cases with the clinical diagnosis of xanthoma juvenile were investigated; all of them confirmed by biopsy and all of them with a normal blood cholesterol content.

The family history in the cases reported in the literature and in this paper was non-contributory. In these children, the clinical picture of the lesions was typical and in all of them, the lesions were single, not forming any clusters, lines or sheets. The distribution was irregular, some of them showing involvement of the skin of the trunk, some of them with more lesions on the forehead and scalp. None of the cases appeared acutely ill at the beginning. In Cases 1 and 2, the lesions appeared at the age of six and eight months, respectively. There was complete well-being and normal development. In Case 1, there were

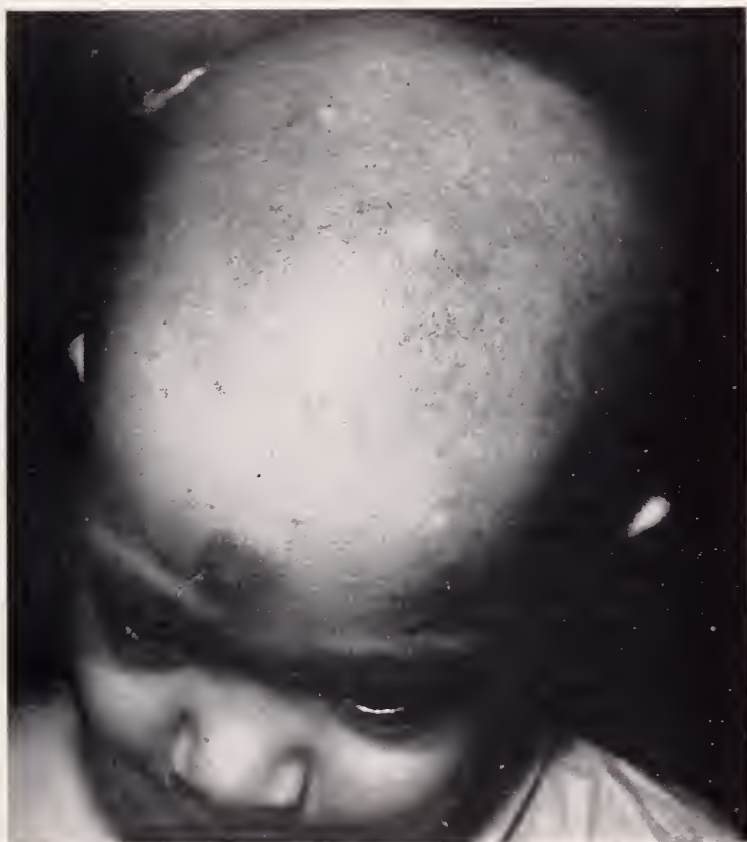


FIG. 1. Single xanthomatous skin lesions on forehead and scalp. Large hemorrhagic lesion on forehead. (P. Freud: *J. Pediat.* 38: 744, 1951).

14 xanthomatous skin eruptions at the age of two years. At the age of three years, only three were left, all of them completely flat with an intense golden maroon coloration. At four years, all lesions had disappeared. In Cases 2, 3, and 4, the lesions have not yet disappeared completely but have diminished in number. The children are doing well and are being checked every six months (clinical examination, x-rays of chest and skeleton).

In Case 5, just four single xanthomatous lesions were seen at the age of five months. At the age of two years, a few more lesions had appeared on the trunk. The patient did well until the beginning of his third year. At this time the parents observed that the child was extremely thirsty and urinated frequently, passing large amounts of water. Laboratory examination at this time revealed a specific gravity of the urine around 1.011; otherwise the urine was normal. Even after restricting fluids for prolonged periods of time, the specific gravity figure of the urine could never be raised higher than 1.012. Blood chemistry was

normal, and the x-ray findings of chest and skeleton remained essentially negative, and no exophthalmos developed. The diagnosis of diabetes insipidus was made. Although the figure of 1.011 is a rather high concentration for this condition, there is no doubt that the child had developed a true diabetes insipidus. This opinion is in agreement with the statement of Thannhauser (22) that anatomical lesions are found in the pituitary stalks or hypothalamic region in these cases. The child is running a downhill course, losing weight and has developed a severe secondary anemia.

Case 6 was admitted to another hospital at the age of 20 months for acute nasopharyngitis, otitis media and disseminated xanthomatosis of the skin. This diagnosis was confirmed by biopsy. At the age of two years, the child came under our observation with the chief

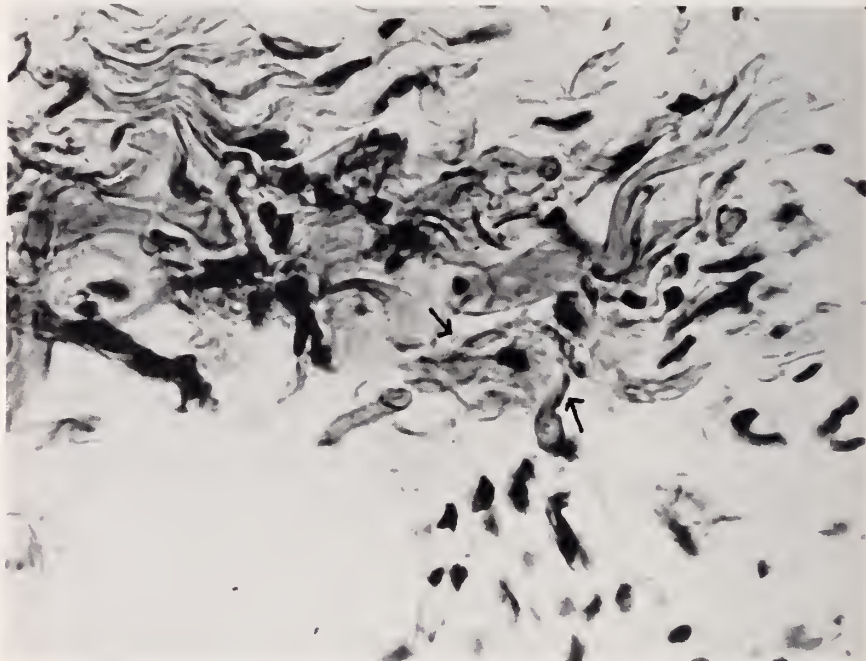


FIG. 2. Large mononuclear foam cells infiltrating the skin. (P. Freud: *J. Pediat.* 38: 744, 1951).

complaints of a cold for one month, abdominal distention, and disseminated xanthomatosis of the skin (fig. 1). The lesions were not too numerous and were singular, distributed over the scalp, face and trunk. Another skin biopsy confirmed the diagnosis of xanthomatosis (fig. 2). Six months later, the child developed lymph gland enlargement but biopsy did not show any significant pathological changes. At this time the infant had also developed the picture of a chronic myelogenous leukemia which is quite unusual for his age group. There was increasing splenohepatomegaly. Only 15 months later, when a lymph gland biopsy was done again, was extensive reticuloendotheliosis found which had changed the normal structure of the lymph node completely (fig. 3). The course of the condition up to January 16, 1951, characterized by remissions and exacerbations, has been described in detail (23). After this date, the child's condition rapidly declined; there developed signs and symptoms of leukemia, severe purpura, heavy nose bleeds and high fever. On June 12, 1951, the child became much weaker, ultimately lethargic and hyper-irritable. There were frequent paroxysms of coughing and several episodes of vomiting. On June 14 and 15, 1951, profuse epistaxis occurred and on the latter date, the child expired after he had lapsed into a convulsive

seizure. The clinical diagnosis of leukemic reticuloendotheliosis was made after due consideration of the xanthomatous skin lesions and lymph gland reticuloendotheliosis found at biopsy. This diagnosis was confirmed by autopsy where profuse reticuloendotheliosis of practically all the internal organs was found. A detailed report on this case will be published soon.

COMMENT

The cases presented in this paper and the cases reported in the literature, in which xanthoma juvenile was accompanied or followed by systemic reticuloendo-

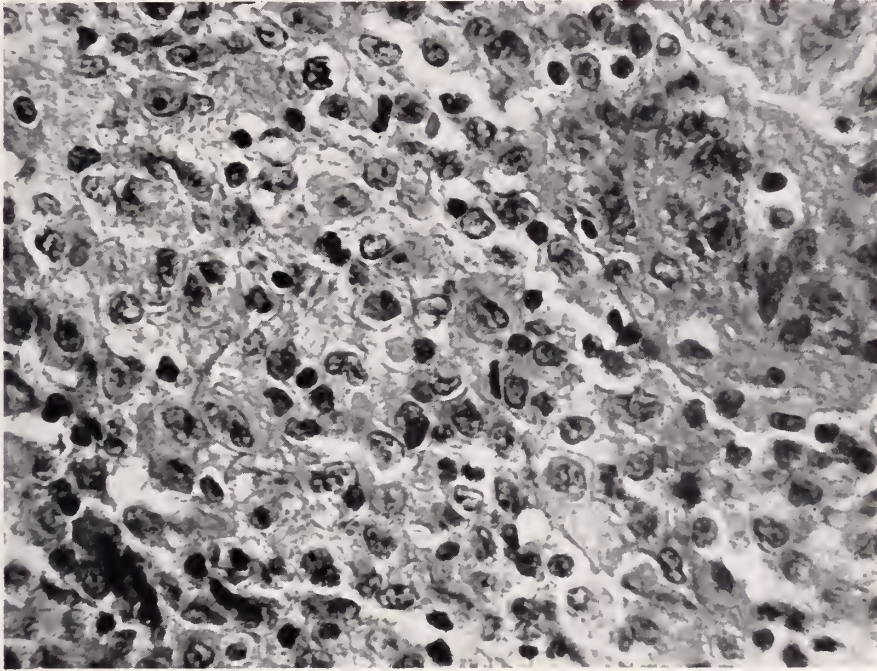


FIG. 3. Lymphnode: Physiological architecture changed by profuse reticuloendotheliosis. (P. Freud: *J. Pediat.* 38: 744, 1951).

theliosis, show that at the present time we have no definite clinical or histological means to predict whether these lesions will remain restricted to the skin and eventually disappear, or whether they will be followed by systemic reticuloendotheliosis. All that is known is that there is a state of increased proliferative activity of the reticuloendothelial system which may subside or lead to generalized pathology.

SUMMARY

1. Xanthoma juvenile, the childhood form of xanthoma disseminatum, is an usually benign, monosymptomatic skin type of systemic reticuloendotheliosis.
2. The possibility of visceral involvement should be envisaged and the children checked at periodic intervals until all skin lesions have disappeared.

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PROBLEMS IN JUVENILE DIABETES MELLITUS*

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Thirty years have elapsed since the discovery of Banting and Best, and yet there are still many unsolved problems in the treatment of juvenile diabetes and much discussion concerning prognosis, complications, psychological problems etc. Assuming an average age of ten years at the onset of the disease in 1921, we are not yet able to answer the question "will the juvenile diabetic live to the present life expectancy of 65.49 years for the male, and 71.04 years for the female." However, the high incidence of complications, particularly of degenerative vascular lesions, does not permit a too optimistic outlook.

Another problem is the occurrence of untoward reactions to the insulin treatment itself. Even with the most careful spacing of meals and injections, insulin reactions are unavoidable. They may occur at any time during the day or night and cause apprehension to patients and parents. Compared with the permanent and well regulated flow of insulin from the islands of Langerhans in the non-diabetic organism, the insulin injection is only a crude attempt at imitating nature. Somogyi (1) has shown that insulin hypoglycemia may be followed by hyperglycemia as a result of an over-active correction process of hepatic glycogenolysis. Thus, patients suffering from repeated insulin reactions are in permanent danger and may be thrown from shock into diabetic acidosis. Electroencephalographic studies have even shown the possibility of brain damage. According to Greenblatt, Murray and Root (2), fifty-one per cent of patients who complained of frequent severe insulin reactions had abnormal electroencephalograms. Reactions to protamine zinc insulin are different from those to the quickly acting insulins. Headache, malaise, nausea and vomiting are in the foreground, rather than trembling, sweating and tachycardia. This particular form of insulin reaction is one of the reasons why younger children are in general easier to regulate on regular or crystalline insulin than on protamine insulin, including the recently introduced NPH insulin.

A third problem in juvenile diabetes is the emotional pattern created by the peculiar life situation with which a diabetic child has to cope permanently. To live on a restricted diet and to know that life depends on a syringe requires a well balanced personality. The attitude of an adult to incurable disease is either strict and painstaking adherence to the doctor's prescriptions and the hope that a miracle may happen, or a more fatalistic point of view with indifference towards all admonitions and warnings. Young children do not grasp the seriousness of the situation. They only realize that they are handicapped by the disease and are at a disadvantage with their contemporaries. Adolescents frequently find themselves in trouble and have to be readmitted to the hospital again and again in diabetic acidosis or in coma as first rate emergencies. Almost invariably die-

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tary excesses are the cause, and not so much omission of the insulin injections. These frequent periods of hospitalization—up to three or four a year—stigmatize the child, make him more and more self conscious about his illness, and separate him from the nondiabetic. School attendance suffers, and the child-parent relationship is usually strained and rather poor. Sooner or later the majority of these offenders learn a lesson, particularly when sexual maturity is reached, but some of them are crippled for life.

From this particular group of juveniles arise the candidates for complications. It has been shown in a recent study on 247 patients by Wilson, Root and Marble (3) that no patients with excellent or good control revealed advanced calcification or retinitis even after periods of twenty to thirty-four years with diabetes. Fifty-five patients among eighty cases who lived for periods of at least twenty years (under poor or fair control) on an unmeasured diet, without constant use of insulin and without constant control of glycosuria, showed severe degenerative lesions (calcified arteries, retinitis, or nephropathy). Similar conclusions were reached by Grayzel and Marshall (4). In a smaller series than the one mentioned above, none of the patients whose control was considered good developed detectable vascular lesions even though suffering the disease for periods ranging from ten to twenty-eight years. These observations are of such importance that we should not change our attitude towards “measured” versus “free” diet.

At the sixth International Congress of Pediatrics in Zürich (1950) the influence of diabetic control on the occurrence of complications was thoroughly discussed. Contradictory conclusions were reached by different investigators. Lichtenstein (5) and Stolte (6) presented some material in favor of a “free” diet. Lichtenstein stated that whether the treatment is with or without restricted diet, retinopathy and nephropathy occur frequently and probably with about the same frequency, but the occurrence of calcified arteries is less frequent in patients treated with a “free” diet than in patients living on a diet restricted in carbohydrates. According to Lichtenstein, neither clinical and experimental experience nor theoretical reasons favor the opinion that a “free” diet increases the appearance of vascular disease in diabetics. Nor is there today any proof that the prevention of vascular disease is possible with good control. Good control of a diabetic child is possible without a diet restricted in carbohydrates. Stolte reached similar conclusions. However, Stolte’s “free” diet is actually a high carbohydrate and a low fat diet, therefore a low caloric diet. Lichtenstein likewise emphasizes the avoidance of over feeding. These diets closely approach what we consider at the present time a balanced diet for a juvenile diabetic, the only difference being that ours is a measured diet. In contrast to Lichtenstein’s and Stolte’s viewpoints, P. White (7) and R. L. Jackson (8) are of the opinion that the level of control is an important factor influencing degenerative changes. A high level of control appears to offer the best means of averting or delaying chronic degenerative changes. Such levels can only be obtained on measured diets.

Our own observation on long standing cases of juvenile diabetes strongly favors the necessity of a measured and well balanced diet. It should be a liberal

diet, and should not be so complicated that a mother unfamiliar with calories and grams of carbohydrate, fat and protein, is unable to feed it to the child. All diets should be prescribed in simple household measures together with an easily understandable table of food equivalents, also in household measures. The patients should be seen in short intervals, and diet as well as insulin readjusted from time to time according to the requirements of the growing child. The most reliable patients overstep their allowance in the course of events so that the measured diet gradually develops into a more or less "free" diet. But there is still a difference in degree. Slight overstepping of the allowance has to be taken into account. It does not do much harm to the child, when insulin is administered permanently in adequate amounts. Only gross excesses have to be avoided. It is not only the carbohydrate tolerance which determines the metabolic situation, but also the total caloric tolerance is important. There is no linear proportionality between carbohydrate ingested and insulin administered. The same amount of carbohydrate given without any other food is tolerated much better than when given with an excess of other calories. This simple interrelation has to be borne in mind in the dietetic treatment of juvenile diabetics.

Some diet offenders and food addicts in the adolescent group still try to compensate for their excesses by increasing the insulin. This is usually futile and finally leads in a vicious circle to complete breakdown and diabetic coma. Only complete food abstinence, with return to the administration of frequent doses of regular insulin and enough sugar to avoid insulin shocks, may save the situation. In case of vomiting, epigastric pains and toxic dehydration, home treatment is no longer possible. Hospitalization and intravenous fluid treatment are necessary.

Sherrill (9) discussed in a recent article the danger of "free" diet in relation to retinal degenerative changes. He presented a group of patients who have been under treatment from twenty to thirty-three years and who have normal vision. They avoided glycosuria and hyperglycemia as consistently as possible during each twenty-four hour period. He states: "One of the weakest alibis offered in support of "free" diet is the fear of neurosis or a dietary complex." "Grave and serious responsibility rests upon the physician who would recommend "free" diet."

Our own material can be subdivided into two groups. One group was studied with R. Priesel in Vienna until the advent of Hitler in 1938, the other in this country. Our first patient (female) is still alive after 27 years of her disease, and has reached the age of 40 years. The only complication in her case is a diabetic retinitis. She was the first juvenile diabetic treated with insulin in Austria. Since at the beginning insulin was not commercially manufactured, each batch had to be called for at the Institute of Pharmacology of the University of Vienna.

The American group consists of thirty-one patients, who were seen in the Boston Floating Hospital since 1942 and followed in the Boston Dispensary. The two youngest patients were sixteen months, some of them were between five and seven years, the majority between nine and twelve years at the onset of the disease. The group is too small for a complete analysis. There were two

fatalities from diabetic coma; one of the two cases was a Mongoloid. NPH insulin was tried in some of our cases. It proved unsatisfactory in long standing cases with a daily insulin requirement of seventy to eighty units. No serious complications have developed so far, except a xanthoma diabeticorum in one girl soon after the onset, and some of the usual behavior disorders.

Of greater interest is the Vienna group. There are two reports available on the Vienna cases and upon their fate, one by E. Pabst (10) and a second by T. Rohrachner (11). According to E. Pabst's report, of sixty-two cases, who were treated from 1923 through 1929 by Priesel and Wagner in the Children's Hospital of the University of Vienna, thirty-nine have survived beyond the twentieth year of their disease; thirty-six (58 per cent) are still alive, from the ages 22 to 40 years, with a duration of the disease from twenty to twenty-seven years. Of the twenty-six fatalities, nine patients died from tuberculosis; in no case has kidney disease been the cause of death. Among the thirty-six survivors, three showed nephrosclerosis and five albuminuria without elevation of the blood pressure or edema. In twenty-two cases the eyes were examined; in the three cases with nephrosclerosis severe degenerative changes of the retina with considerable visual impairment were detected, in eleven cases retinal hemorrhages, in none of the cases sclerosis of the retinal arteries. Only seven of the twenty-two cases did not show any complications. All the patients were on a carbohydrate low regime until 1929, later on a high carbohydrate diet.

Rohrachner's report on the Vienna juvenile diabetics is more complete. From 1923 to 1935, 192 children and juveniles were under care. According to a survey of Priesel (12) in 1935, 189 cases could be traced. Two girls showed pulmonary tuberculosis; 168 children were alive, free of complications and in good general condition; and 19 (10 per cent) were dead. Rohrachner's report deals with the fate of 124 cases of the entire group of 192 cases. Why a relatively large number of cases (68) could not be traced is explained by the political events in Austria since 1938. Of the 124 patients with onset of the disease in the years 1922 to 1935, sixty-six (53 per cent) were alive, and fifty-eight (47 per cent) dead as of January 1950; thirty-eight of the survivors have been diabetics for more than twenty years. The causes of death were: diabetic coma in twenty-three cases; tuberculosis in eighteen cases; nephropathy in two cases; sepsis in five cases; other intercurrent illness in eight cases; a war casualty in one case, and unknown cause in one case. In the first five years of the disease more than half of all fatalities could be attributed to diabetic coma. The death rate from tuberculosis was almost as high as that from diabetic coma, much higher than in other statistics. On the other hand, the death rate from nephropathies was rather small, with only two fatalities after a duration of diabetes from fifteen to twenty years.

It is interesting to compare the death rate of the Vienna diabetics with that of the Boston cases in 1946 under the care of P. White (13): "Of the 2191 diabetic children 1774 are living and 385 have died, 221 in the insulin era. As deaths from coma and sepsis are falling, those due to vascular disease have increased. Deaths from coma are commonest in short duration cases accounting for more than half of the deaths occurring under five years of the disease. After fifteen years of diabetes half of the deaths are due to nephritis. Until 1930, coma deaths

far out-numbered all others. From 1930 to 1936 deaths due to infections approached those due to coma. Between 1940 and 1946, nephritis has become the chief cause of death in patients with onset of diabetes in childhood."

This discrepancy in the mortality rate and causes of death of the Vienna and Boston diabetics (47 and $17\frac{1}{2}$ per cent) needs some further explanation. In the first place, the Vienna group is smaller. Even if there were included the private patients who were under the author's care from 1923 to 1938 without any fatality, the death rate would still be more than twice as high. The high mortality rate from tuberculosis (9.5 per cent in Boston vs. 31 per cent in Vienna) is well explained by greater exposure. We need not resort to a concept of higher susceptibility or a stormier course of tuberculosis. More difficult to interpret is the low mortality from kidney disease in the Vienna group. According to Rohrachner's interpretation, there is a difference in the dietetic treatment and general management of the patients admitted from 1922 to 1929, and those admitted from 1930 to 1935. The former group was kept on a low carbohydrate and high fat regime, the latter on a higher carbohydrate and low fat regime. Both fatalities from kidney disease occurred in the second group. The number is rather small for statistical studies. However, if the mortality of both groups is compared after ten and fifteen years of the disease, there was in the first group a mortality of six out of forty-seven survivors (13 per cent) during the last five years of the observation period, in contrast to thirteen fatalities out of forty survivors (32.5 per cent) in the second group. One has the impression that with about the same *early* mortality in both groups, the *ultimate* fate of the first group is more favorable. Rohrachner concluded that the first group was from the start better disciplined and so well indoctrinated that the patients were in a more favorable situation when entering the danger zone.

Thus patients and parents learned what they could do to avoid trouble. Assuming that self discipline and strict adherence to diet, independent of the arrangement of the diet, and permanent insulin treatment in sufficient amounts, are the limiting factors to developing serious and always fatal kidney damage, the prognostic outlook for survival of the juvenile diabetic is rather favorable. One of the other two killers, the diabetic coma, seems to be avoidable; the other, tuberculosis, is environmentally conditioned and may be entirely extinguished in the course of the next decades. In this country there is such a marked decline in the number of tuberculin positive children that the National Association for the Prevention of Tuberculosis predicts the disappearance of the disease within the next 75 years.

Here we come to an important problem in the care of the juvenile diabetic. Speaking of discipline and indoctrination, in the case of diabetes we are dealing with incurable disease, but not an incurable disease comparable to other ailments. There is hardly any other disease where neglect, and mistakes in the care and treatment of the uncomplicated form, precipitate so obvious reactions. The boundary between life and death is narrow. The juvenile diabetic resembles a mountain climber walking on a narrow, icy ridge. One wrong step, and he goes down into the abyss. Only when he is on the rope is he safe.

We do not yet know how to avoid complications and what is the best manage-

ment in attempting prevention. There are investigators who are of the opinion that untoward sequelae cannot be prevented, because the tendency to complications, particularly degenerative vascular lesions, is established in the specific "anlage" of the diabetic. Grayzel and Marshall (4) rightfully pointed out that "no juvenile diabetic patient, even with the assistance of present-day insulin and prescribed diet, can respond in a completely physiologic manner to his food intake, activity, etc." For this reason it is still more important to help the patient in approaching what we consider a normal metabolic balance, by close and permanent follow-up and advice.

In a democratic society the physician's supreme duty is to preserve individual life, independent of eugenic considerations. No deviations are permissible. In a totalitarian society with its lack of respect for the individual and with the latter's subservience to the state, we have seen how easily the medical profession can become infested with phantastic pseudo-eugenic ideas. It is difficult to prove, but this might well be one factor responsible for the higher mortality of the Vienna diabetics.

In addition to his physical care, the juvenile diabetic needs more guidance than the non-diabetic from the psychological viewpoint. Most of his problems are closely related to stealing food or money in order to buy some of the forbidden fruits, such as candy, ice cream, soft drinks etc. These transgressions, particularly when occurring in the younger age group, must not be taken too seriously, as they happen more or less in all cases and should be attended by the physician responsible for the diabetic care. In the adolescent group other problems become acute. Dietetic excesses, occasionally overcoming the patient like an addiction, are usually within an higher order of magnitude than in the young child. In addition, the physiological emotional instability of puberty is aggravated by the peculiarity of the disease and the artificiality of the existence. The natural separation from the family in this age group and the tendency to become independent, lead occasionally to complete refusal of accepting intra-familial guardianship and to rebellious outbursts against the authority of the parents. It is within the scope of a well organized social service, familiar with diabetes in childhood and adolescence, to help and even to resort occasionally to placement in a good environment, if the family cannot cope with the situation. In general such cases are rare, and only in one instance during the last ten years was it necessary to place a child of eleven years in a mental hospital. This patient was a fire-setter and so dangerous to his environment that no other placement could be considered. At the age of sixteen years he was discharged and is at the present time under the care of the Preventive Clinic of the Boston Dispensary.

The mental capacity of juvenile diabetics is within normal range. They are not often of superior intelligence, as was erroneously assumed. However, gross mental retardation is rare, and in general the distribution of mental abilities is comparable to that in a non-diabetic group.

So much on the clinical aspects of diabetes in childhood. Joslin has called diabetic children "explorers of uncharted seas." By Banting and Best's discovery we became familiar with conditions heretofore unknown. It is the patient him-

self who contributed to our knowledge of childhood diabetes, by surviving into a period of life which was unattainable territory prior to 1921.

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SERUM AND HEPATIC ENZYMES IN EXPERIMENTAL LIVER DAMAGE*

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Many of the serum enzymes are mainly or solely of hepatic origin. Variations of their serum level in liver disease are being studied in the attempt to obtain diagnostic criteria for hepatic damage. As the knowledge of serum enzymes increases the role of serum enzyme determinations as hepatic function tests seems to gain importance. This is shown by the emphasis placed on serum alkaline phosphatase (1) and on serum cholinesterase (2, 3). The relation between serum and hepatic enzymes is complex. The liver cell contains a large number of enzymes acting upon a great variety of substrates; many, especially the respiratory enzymes, are found in other organs as well. It appeared of interest to investigate in the rat the relation between serum and hepatic enzyme activities in several types of acute and chronic hepatic injuries (including liver cell damage and/or fatty changes) and to observe the variations of the serum enzymes in the same animal during the acute intoxication. Alkaline phosphatase and esterase were chosen in view of their clinical significance. Rat serum contains in addition to the non-specific (pseudo-) cholinesterase (the only one found in the human) specific (true) cholinesterase (4). Therefore phenyl-benzoate, a substrate for non-specific esterase, was used. It has been shown in this laboratory (5) that determinations with phenyl-benzoate and acetylcholine give parallel results in human serum. As a rule respiratory enzymes are absent from serum. Xanthine oxidase is an exception being present in rat and guinea-pig serum (6). This enzyme therefore was also studied.

An extensive literature deals with the activities of alkaline phosphatase in serum and liver. It has been found increased in damaged liver tissue (7, 8). In serum it has been found slightly increased in parenchymal liver damage and markedly increased in biliary obstruction (1). It was found to decrease in severe hepatic failure (9). Esterase has been found reduced in liver tissue (10) and serum (2, 3) in hepatic damage.

MATERIAL AND METHODS

For the first part of this study 60 white, Wistar strain, female rats, weighing from 175 to 210 g were used. They were divided into 2 groups, 28 for the acute and 32 for the chronic experiments. In the acute experiments the rats were fasted for 16 hours before the intoxication and throughout the experiment;

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they were divided into 4 subgroups; one remained fasted but untreated as control, the other 3 received per 100 g body weight intraperitoneally a) 0.03 ml. of carbon tetrachloride in 0.3 ml. mineral oil, or b) 0.05 ml. of bromobenzene in 0.25 ml. olive oil or c) 100 mg. of ethionine dissolved in 4 ml. of water with sodium carbonate and given in 3 doses 2 hours apart. The animals were killed by bleeding from the abdominal aorta under short alcohol-ether anesthesia 48 hours after the administration. For the chronic experiments the animals were fed a synthetic diet consisting of 15 per cent casein, 76 per cent sucrose, 6 per cent corn oil and vitamin and salt supplements. One subgroup received this basic diet alone. The diets of the 3 others contained a) 5 per cent carbon tetrachloride or b) 5 per cent bromobenzene or c) 0.5 per cent ethionine. The animals received the diet twice a day to avoid the evaporation of the halogenated compounds. The control group and groups a) and b) were killed after 8 weeks, while the ethionine-fed animals were killed after 5 weeks. Histological examinations were performed and esterase with phenyl-benzoate as substrate (11) and alkaline phosphatase (12) were determined in liver homogenates (1/20) and serum. Xanthine oxidase was determined in serum according to the method of Blauch et al. (13), using Browns reagent for the uric acid determination (14).

For the second part, 14 white, Wistar strain, female rats weighing from 205 to 228 g were fasted throughout the experiment and divided into 3 groups. One was left untreated as control. The 2 others were intoxicated with carbon tetrachloride and bromobenzene as mentioned above. Before and 6, 12, 24, 48, 72, 96 and 120 hours after the administration esterase, alkaline phosphatase and xanthine oxidase were determined in blood obtained by cardiac puncture.

RESULTS

Serum and hepatic enzymes in acute hepatic injury. After 48 hours the livers of the rats treated with carbon tetrachloride showed acidophilic necrosis of the centro-lobular zone with extensive disappearance of parenchymal cells and moderate Kupffer cell mobilization. In the intermediate zone fatty metamorphosis and a few large hydropic liver cells were noted (fig. 1A). In comparison to the controls esterase activity was markedly decreased in the liver, but showed a normal mean value in the serum with an unusually high standard deviation indicating a wide spread of individual results (table 1). Alkaline phosphatase was high in liver and serum. The serum xanthine oxidase was significantly higher than in the controls, again with a large standard deviation. The livers of the bromobenzene treated rats revealed, as described (15), necrosis of the centro-lobular zone with disappearance of individual or groups of liver cells (occasionally associated with collapse), some proliferation of Kupffer cells and infiltration with pigment containing histiocytes. On the border of the necrotic zone, cells with hydropic or with diffuse acidophilic cytoplasm were noted. Fatty metamorphosis was absent (fig. 1 B). The alterations of enzyme activities in liver and serum were similar as in carbon tetrachloride intoxication, though less pronounced. The standard deviations for serum esterase and xanthine oxidase were large. Ethionine, a presumed antagonist of methionine (16) produced in female

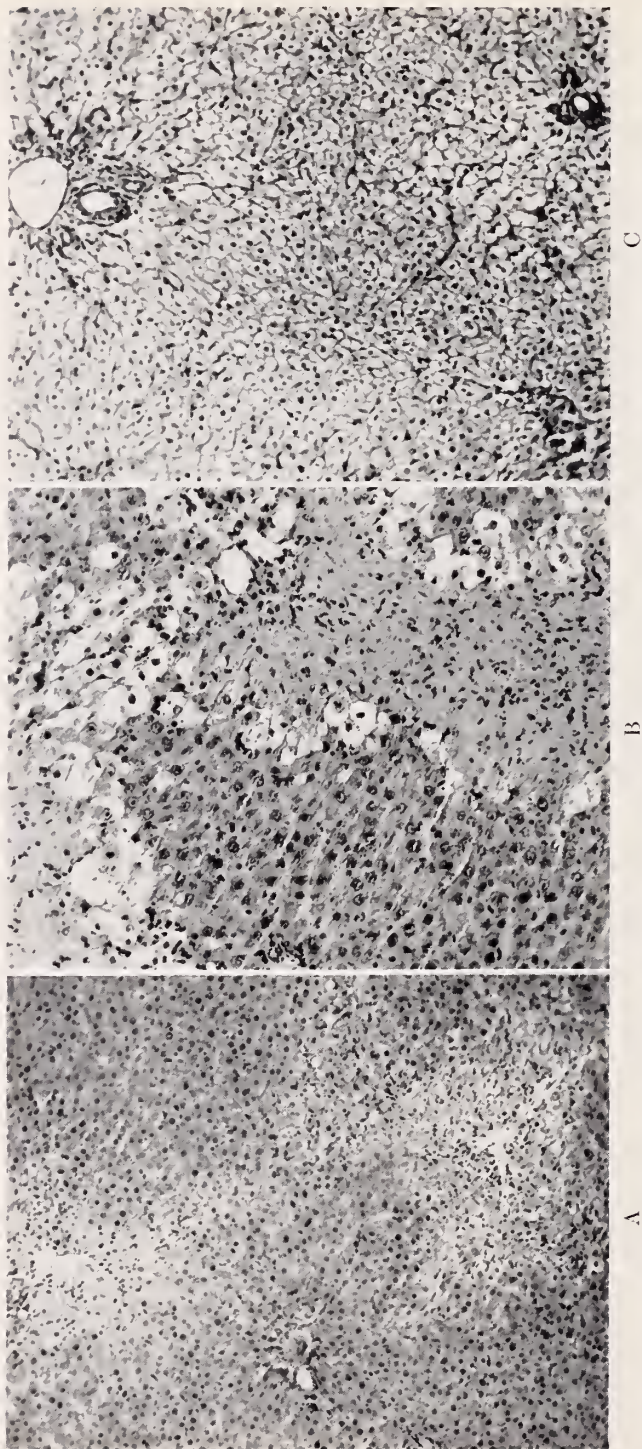


FIG. 1. Photomicrographs of rat livers: A. Acute carbon tetrachloride intoxication. Necrosis and disappearance of liver cells and proliferation of Kupffer cells in the centro-lobular zone. Hydrotic swelling and fatty metamorphosis in the intermediate zone. B. Acute bromobenzene intoxication. Acidophilic necrosis and partial disappearance of the liver cells in the centro-lobular zone. Accumulation of histiocytes around the central veins. Hydrotic swelling of liver cells on the border of the necrosis. C. Acute ethionine intoxication. Diffuse fatty metamorphosis.

rats (17) a marked diffuse fatty metamorphosis without significant necrosis or other evidence of liver cell damage (fig. 1 C). The results of the enzyme determinations did not differ from those of the controls.

Serum and hepatic enzymes in chronic hepatic injury. The control animals on the synthetic diet showed a histologic picture of the liver and enzyme findings no different from animals on stock diet. After prolonged carbon tetrachloride feeding the liver exhibited a beginning distortion of the lobular pattern produced by connective tissue septa connecting the central fields and occasionally these with the portal canals. The liver cells revealed different degrees of damage and focally extensive fatty metamorphosis (fig. 2 A). Esterase was markedly decreased and alkaline phosphatase increased in liver and serum. Xanthine oxidase was increased, but without statistical significance. After chronic feeding of bromobenzene the livers showed an alteration of the cytoplasmic staining, which was

TABLE 1

Alterations of serum and hepatic enzymes in correlation with cell damage and fatty metamorphosis (as seen histologically) in acute and chronic hepatic injury

TYPE OF INTOXICATION	NO. OF ANIMALS	HISTOLOGIC		ESTERASE		ALKALINE PHOSPHATASE		XANTHINE OXIDASE
		Liver cell damage	Liver fat	m Mol./hr./g wet liver	m Mol./hr. 100 ml. serum	μ Mol./hr./g wet liver	μ Mol./hr./100 ml. serum	μ Mol. oxidized/hr./100 ml. serum
Stock diet controls	7	0	0	1.50 \pm 0.36	6.2 \pm 0.85	19.8 \pm 5.4	250 \pm 32.4	120 \pm 15.6
Acute CCl ₄	7	++	++	0.56 \pm 0.23	6.3 \pm 3.35	112.4 \pm 16.4	623 \pm 63.0	370 \pm 145.4
Acute Bromobenzene	7	++	0	0.84 \pm 0.34	7.5 \pm 4.02	86.5 \pm 14.6	466 \pm 71.6	267 \pm 158.6
Acute Ethionine	7	0	+++	1.68 \pm 0.43	5.8 \pm 0.36	23.3 \pm 3.9	295 \pm 38.6	148 \pm 48.5
Synthetic diet controls	9	0	0	1.22 \pm 0.26	4.7 \pm 0.56	22.3 \pm 4.1	246 \pm 24.5	145 \pm 18.4
Chronic CCl ₄	7	++	++	0.59 \pm 0.19	2.8 \pm 0.62	73.5 \pm 15.6	760 \pm 80.3	182 \pm 31.6
Chronic Bromobenzene	8	+	0	0.73 \pm 0.42	3.2 \pm 0.58	61.4 \pm 23.6	632 \pm 81.4	176 \pm 43.4
Chronic Ethionine	8	+++	0	0.31 \pm 0.18	1.5 \pm 0.65	102.0 \pm 14.4	923 \pm 67.5	205 \pm 54.3

less marked in the central zone. In the peripheral zone the cytoplasm appeared hydropic and contained coagulated clumps. The liver cell plates were irregularly arranged, but the lobular architecture was intact. No increase of fat was noted (Figure 2 B). The enzyme changes were similar to those after carbon tetrachloride feeding. Prolonged feeding of ethionine (18) produced severe diffuse liver cell damage with necrosis of isolated cells or small groups of cells. The liver cell damage was more severe than in any other group. Extensive fibrosis separated individual cells or groups of cells. Large nuclei and nucleoli indicated attempt at regeneration. There was new formation of reticulum fibers and infiltration by histiocytes as well as proliferation of cholangioles. In places the lobular architecture was distorted. Fat was absent from the liver cells and only a few droplets were found in the Kupffer cells (Figure 2 C). The esterase activity was significantly lower in both liver and serum than in the other intoxications and the alkaline phosphatase activity was higher in both, although in the case of the alkaline phosphatase the difference from the other intoxications was less striking.

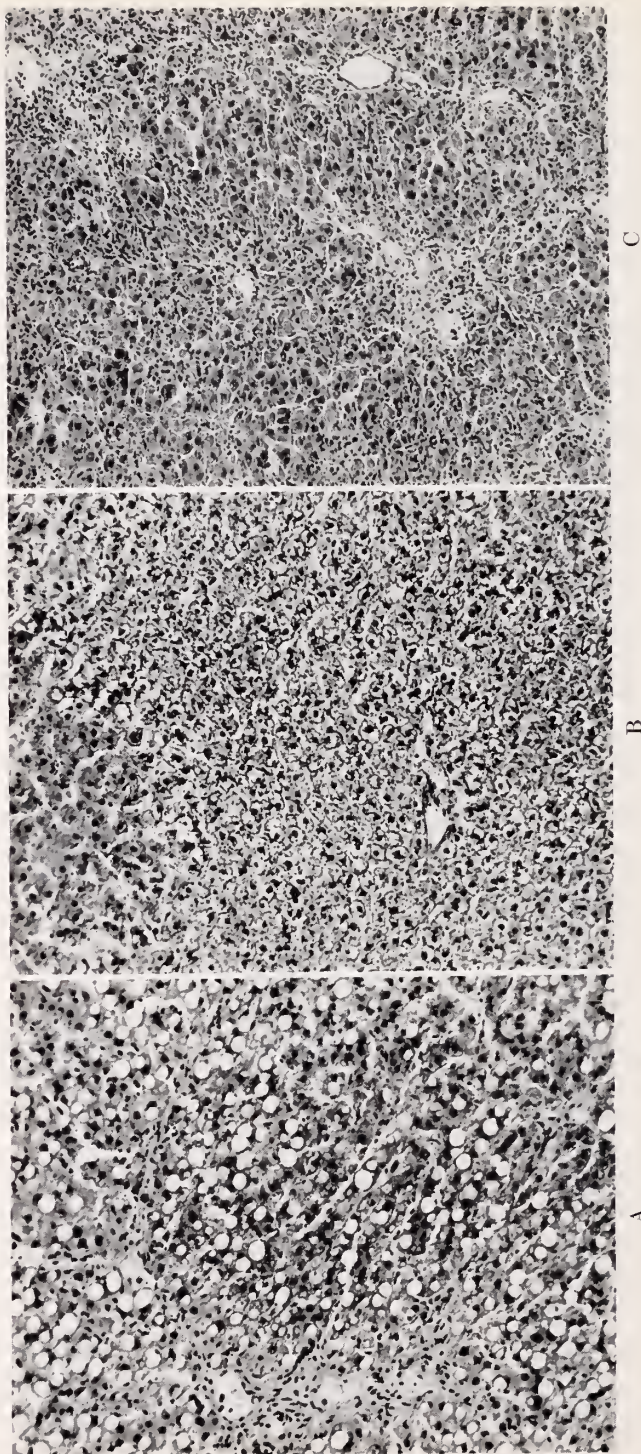


FIG. 2. Photomicrographs of rat livers: A. Chronic carbon tetrachloride intoxication. Connective tissue septa connecting central fields distort the lobular pattern. Many liver cells are loaded with fat. B. Chronic bromobenzene intoxication. Distortion of the liver cell plates, and hydropic swelling as well as clumping of cytoplasm of the liver cells, chiefly in the intermediate and peripheral zone. C. Chronic ethionine intoxication. Irregular shape and staining qualities of cytoplasm and nuclei of liver cells. Individual cells or groups of cells are separated by fine connective tissue strands containing histiocytes, and in places proliferated cholangioles. Focal areas of collapse and distortion of lobular pattern.

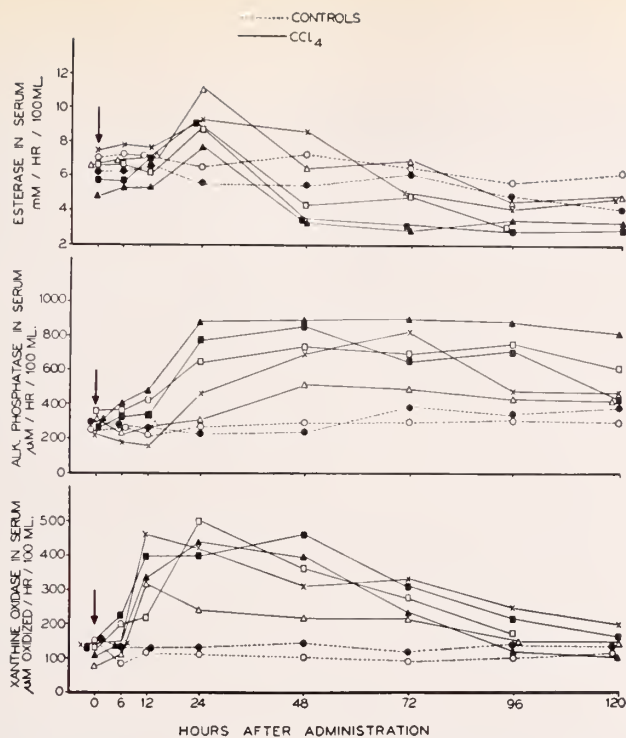


FIG. 3. Variation of enzyme activities in the serums of 2 control rats and of 5 rats following intraperitoneal administration of carbon tetrachloride.

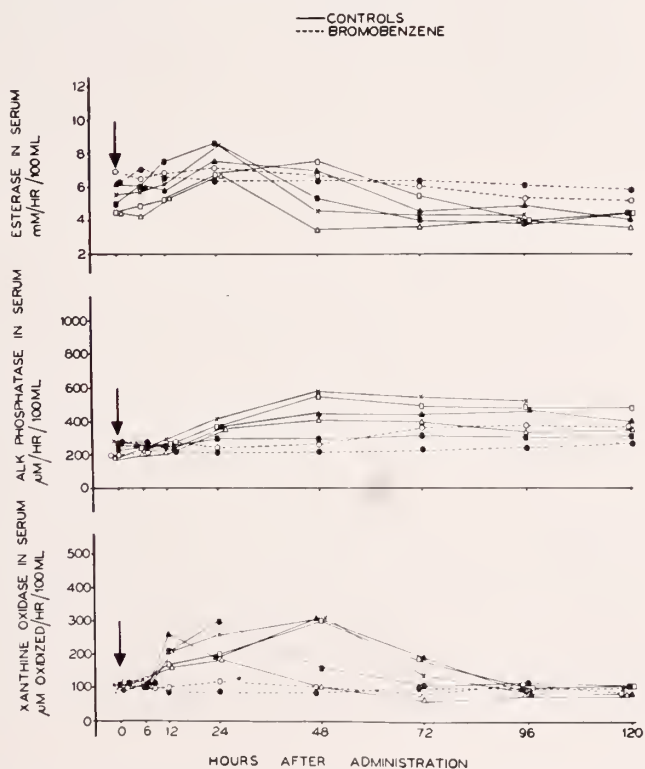


FIG. 4. Variations of enzyme activities in the serums of 2 control rats and of 5 rats following intraperitoneal administration of bromobenzene.

Xanthine oxidase activity in serum revealed a tendency to be higher, but the difference was not statistically significant.

Variation of serum enzyme activity in acute hepatic injury. Serial determinations of the activity of serum esterase after acute carbon tetrachloride and bromobenzene administration revealed an elevation in the first hours, reaching a peak in 24 hours (figs. 3 and 4). This was not noted in the controls. After 48 hours the serum esterase activity was lower than after 24 hours in almost all animals. It dropped further and after 5 days it was below the pre-intoxication level. The serum alkaline phosphatase activity rose in both types of intoxication considerably above the pre-intoxication level. After carbon tetrachloride administration the rise was usually maximal after 24 hours, whereas after bromobenzene treatment it was maximal after 48 hours. In both types of intoxications the elevation was maintained throughout the entire experimental period and even after 5 days the activity was higher than before the intoxication in most instances. Only one animal treated with bromobenzene did not exhibit a significant rise. The xanthine oxidase activity rose rapidly following administration of either carbon tetrachloride or bromobenzene, the rise being maintained for at least 2 days. The activity returned to approximately pre-intoxication levels within 5 days.

DISCUSSION

The studies presented reveal a fairly good correlation between the degree of liver cell damage and the reduction of serum and hepatic esterase and elevation of serum and hepatic alkaline phosphatase. The abnormality of the enzyme activities is most marked in rats chronically intoxicated with ethionine which show the highest degree of liver cell damage. Fat accumulation in the liver appears to have no influence upon the enzyme activity (in keeping with previous observations in this laboratory (19)). Acute ethionine intoxication producing severe fatty liver does not alter the enzyme activities. Moreover in acute and chronic carbon tetrachloride intoxication which produces liver cell damage with fatty metamorphosis, the activities are of the same magnitude as in bromobenzene intoxication without fatty changes.

The relation between serum and hepatic enzyme activity is not clear. In both acute carbon tetrachloride and bromobenzene intoxication the serum esterase levels reveal a wide spread indicated by the very large standard deviation. The serial determinations of the serum enzyme activities in the same rats during acute intoxications clarify this finding. In the initial stage the serum esterase activity rises to markedly elevated levels. Later it drops to values below those of the pre-intoxication level. However, this occurs at different times in different animals explaining the wide standard deviation of determination at 48 hours. In view of the significant reduction of the hepatic esterase activity while the serum esterase is still high it appears justified to assume that the damaged liver releases more esterase than the normal liver. Subsequent to the reduction of the hepatic esterase the serum esterase becomes abnormally low, as it is seen in chronic hepatic injury.

A similar initial rise is noted in the case of xanthine oxidase. Subsequently,

however, the serum activity does not drop below pre-treatment level, but, if anything, is increased in the chronic intoxications. Since hepatic xanthine oxidase activity was not determined, no conclusions can be drawn as to the mechanism of the rise of xanthine oxidase in acute hepatic injury. Possibly a similar release mechanism exists. The lack of depression in the chronic stage could be explained either by an association with regenerative processes in the liver which are very marked, for instance, after chronic ethionine feeding, or by formation of xanthine oxidase in locations other than the liver. Xanthine oxidase has been found in the kidney by one method (20) but not by another (21).

In the case of alkaline phosphatase the serum enzyme activity also rises very markedly during the acute intoxications. Here, however, increased formation in the liver is the probable cause in view of the simultaneous elevation of alkaline phosphatase activity in the liver.

The characteristic difference in the behaviour of esterase and alkaline phosphatase in experimental liver damage are probably related to their location in the liver tissue. Esterase has been found in the cytoplasm (22), specifically in the microsome fraction (23). Alkaline phosphatase, in contrast, in most species is not found within the liver cells, but chiefly in bile capillaries and bile ducts and occasionally in the sinusoids (24, 25). In hepatic damage, however, alkaline phosphatase has been noted in increased amounts, even in the necrotic parenchymal cells (7, 8, 26). The cause of this elevation of alkaline phosphatase in both hepatic damage and biliary obstruction is still argued (9) and it is undecided whether increased formation or decreased excretion of alkaline phosphatase by the liver explain these findings. The temporary increase and subsequent fall of serum esterase observed in these experiments in acute hepatic injury may have clinical significance. It suggests that serial determinations of serum esterase should be done if diagnostic confusion results from normal or elevated values when depressed activity is expected.

SUMMARY

In rats with acute hepatic injury produced by administration of carbon tetrachloride and bromobenzene, the hepatic and serum alkaline phosphatase activities are significantly increased. The hepatic and serum esterase is markedly reduced. Serum esterase (and serum xanthine oxidase) rise immediately following carbon tetrachloride and bromobenzene intoxication probably due to loss from the damaged liver. The serum esterase subsequently drops to levels below those obtained before the intoxication. In acute ethionine intoxication which produces a fatty liver the hepatic and serum enzymes are normal. In chronic carbon tetrachloride, bromobenzene and ethionine intoxication, each associated with liver cell damage, serum and hepatic esterase are consistently reduced and alkaline phosphatase consistently elevated. The elevation of serum xanthine oxidase was not statistically significant. The reduction of serum and hepatic esterase and the elevation of the alkaline phosphatase parallel the degree of liver cell damage and are not influenced by fatty metamorphosis. The difference in the behavior of esterase and alkaline phosphatase is tentatively explained by the fact

that the former is predominantly located in the liver cells whereas the latter is not. Serum enzyme determinations may mirror the degree of liver cell damage; however, in the case of esterase this relation is obscured in the first few days of hepatic injury because the loss of enzymes from the liver produces a temporary abnormal elevation. This may have clinical significance.

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ON THE INCIDENCE OF CARCINOMA IN CHRONIC ULCERATIVE COLITIS

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Carcinomatous transformation of multiple (familial) polyposis of the colon has been known for a great many years. As early as 1895, Hauser (1) emphasized that as a rule this type of polyposis undergoes malignant transformation. Although chronic ulcerative colitis is by no means a newly discovered disease entity, the occurrence of carcinoma in this disease has been described only in recent years. It seems strange that malignant transformation of chronic ulcerative colitis has been observed only recently, whereas observations on carcinoma, developing in familial polyposis, were recorded more than 50 years ago.

Ewing's observation (2) that "carcinoma very seldom develops in chronic ulcerative colitis" seems to be confirmed by the report of Felsen and Wolarsky (3) who did not find a single instance of carcinoma among their 855 cases of ulcerative colitis. On the other hand Cattell and Sachs (4) reported that malignant degeneration occurred in seven per cent of their cases, and Sloan, Bargent and Baggenstoss (5), in about five per cent of 2000 cases observed at the Mayo Clinics.

These differences can be explained in various ways.

1. ULCERATION PROXIMAL TO A STENOSING LESION OF THE COLON

It hardly seems necessary to emphasize that ulceration of the colonic mucosa proximal to a stenosing lesion should be interpreted as inflammation secondary to the stenosis. This occurs whether the stenosing lesion is benign or malignant. Examples of chronic ulceration of the colon proximal to a stenosing carcinoma are presented in Figure 1 (A. 11569, Case 1) and Figure 2 (A. 12883, Case 2). The ulcerations which develop proximal to a stenosing lesion are by no means always extensive. In the two cases mentioned, they are chiefly limited to the area of the distended colon. These cases were observed at the autopsy table, and there is no question as to the secondary nature of the ulceration. If in these patients the colon had been resected surgically, the resected specimen might have been interpreted as an example of chronic ulcerative colitis followed by carcinoma, since the ulcerative lesion and the carcinoma are present simultaneously in a single specimen. This would have been particularly true of Case 2, because in this instance the ulcerative process was very severe. There are also other sources of possible error. When in a patient with a history of longstanding chronic ulcerative colitis multiple carcinomas of the colon develop, then the possibility that this is representative of a malignant transformation of an underlying ulcerated, multiple (familial) polyposis must be considered. These difficulties in the interpretation of individual cases may well explain the divergence of opinion concerning the incidence of carcinoma in ulcerative colitis.

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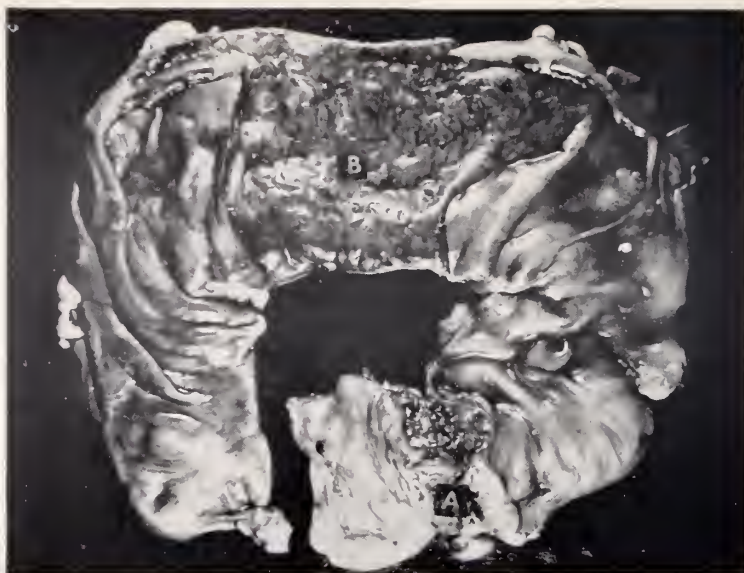


FIG. 1. (Case 1) A. shows stenosing carcinoma. B. indicates localized ulcerative colitis, proximal to constricting portion of colon.



FIG. 2. (Case 2) A. indicates carcinoma. B. dark mucosa indicates ulcerative lesion of colon.

II. MULTIPLE POLYPOSIS (FAMILIAL) WITH MALIGNANT TRANSFORMATION AND CHRONIC ULCERATIVE COLITIS

It is well known that patients with multiple familial polyposis frequently develop severe ulcerative colitis. Sometimes the multiple polyposis is discovered only after the signs of ulcerative colitis have drawn attention to the intestine.

The tendency to development of ulcerative colitis in the presence of multiple polyposis is well illustrated by the following observations.

Many years ago food poisoning led to an epidemic of diarrhea among a hospital staff. All staff members recovered uneventfully in a short time, except for one student nurse. She developed severe symptoms of colitis and finally succumbed. The necropsy disclosed that she was suffering from a widespread multiple polyposis in addition to a necrotizing acute ulcerative colitis. In this case the same intestinal infection which was easily overcome by the normal intestinal tract of the other hospital employees, caused a fatal ulcerative colitis in a patient with familial polyposis.

Figure 3 shows the autopsy findings in a 23 year old male, Case 3, (A. 12613), who had presented symptoms of colitis for at least 6 years. At autopsy an extensive multiple polyposis of the colon with multiple foci of carcinomatous trans-

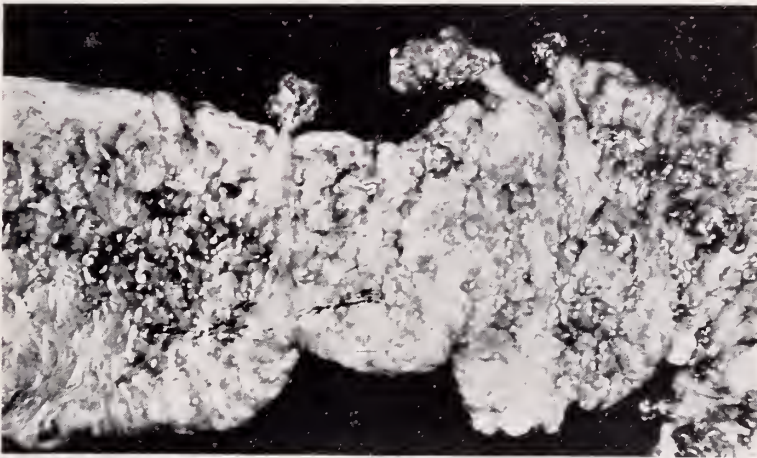


Fig. 3. (Case 3) Part of colon with mushroom-like pedunculated polypi

formation was discovered. Numerous adenomatous polypi varying in shape and size were found, together with mushroom shaped pedunculated polypi. The remaining colonic mucosa showed the chronic (healed) and acute ulcerative lesions commonly present in cases of chronic ulcerative colitis. In this case the presence of many still recognizable polypi, which had not been destroyed by the recurring ulcerative colitis, readily permitted the diagnosis of multiple familial polyposis. Since the patient had been suffering from colitis for at least 6 years, the colonic mucosa presented various changes; the part of the mucosa which was not ulcerated appeared atrophic. In addition to the adenomatous polypi, inflammatory polypi were also encountered.

These two kinds of polyps can be differentiated in the following way. Familial adenomatous polypi are usually mushroom shaped while simple inflammatory polypi caused by longstanding ulcerative colitis exhibit a different delicate bean-sprout-like shape. When, in a given case, inflammatory polypi are not pedunculated, gross inspection is not sufficient to distinguish between inflammatory and

familial polypi. This differentiation is, however, easily made by microscopic study. As shown in Figure 4a, inflammatory polypi seen in longstanding ulcera-

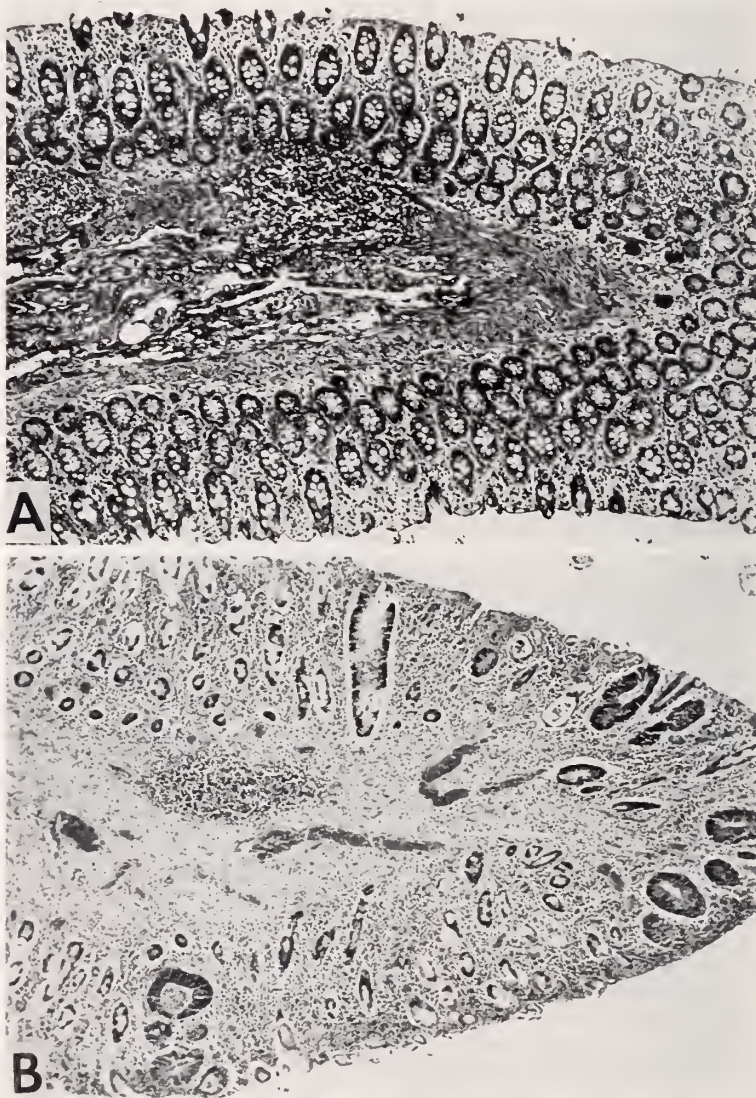


FIG. 4. A. shows typical inflammatory polyp found in case of chronic ulcerative colitis; covering mucosa consisting of low, but normal mucosa. B. (Case 3) shows a typical polyp of familial polyposis in which a number of dedifferentiated glands can be seen.

tive colitis are covered by low colonic mucosa, whereas in adenomatous polypi, areas of "dedifferentiation" (fig. 4b) are always present among the normal mucous glands. In familial polyposis, superimposed areas of ulcerative colitis may heal, leaving grossly atrophic mucosa in which occasional areas of dedifferentiation of mucous glands (fig. 5b) are still encountered.

Such findings were discovered at the autopsy of a 24 year old male, Case 5, (A. 12996). His colonic symptoms had started at the age of 7, when he noted the onset of 5-6 loose stools per day. Bouts of diarrhea recurred frequently and gradually the clinical picture of chronic ulcerative colitis developed. Necropsy revealed an extensive ulcerative colitis which involved the entire colon except for

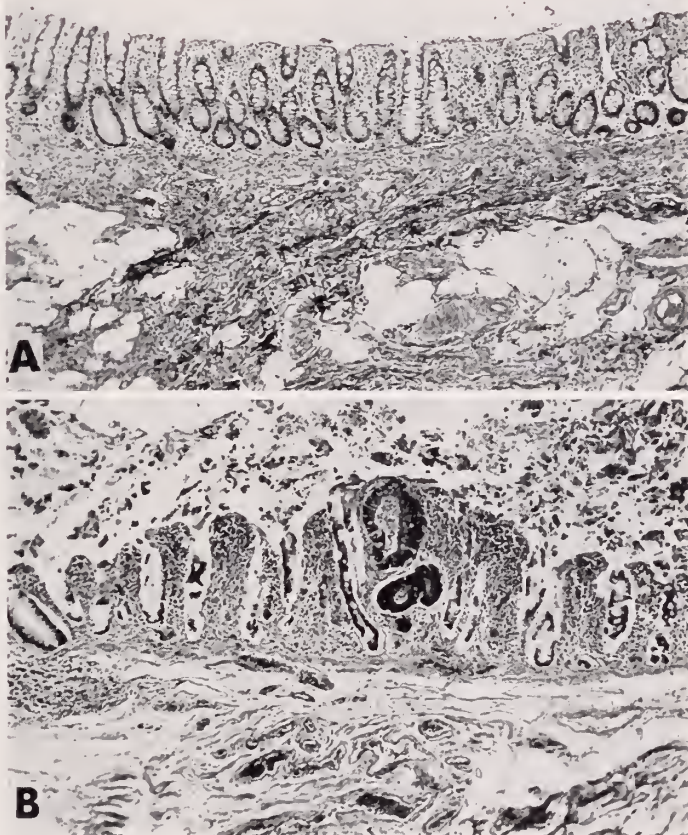


FIG. 5. A. shows healed chronic ulcerative colitis. Note low mucosa and fibrosing submucosa. B. (Case 3) shows the same lesion as A., however, dedifferentiated glands can be seen in the center, a characteristic finding in cases of familial polyposis.

the cecum and ascending colon. In the cecum, a group of polypi were gathered in the form of a "Rasen Polyp" (fig. 6a, b). In the other parts of the colon only a few small pedunculated polypi were discovered. Notwithstanding these gross findings microscopic examination proved these pedunculated polypi to be adenomatous and not inflammatory in nature. It was felt that, in this case, numerous pre-existing polypi had been destroyed by the severe ulcerative process in the colonic mucosa. Three carcinomatous areas could be recognized by gross inspection and on microscopic examination numerous areas of carcinomatous trans-

formation were found through the entire colon. The atrophic mucosa of the healed ulcerative colitis contained dedifferentiated glandular structures in various places (fig. 7a). In some areas, these dedifferentiated glands showed early malignant changes (fig. 7b). Although in this case only a small number of adenomatous polypi were found in the colon, it is obvious that the patient had been suffering

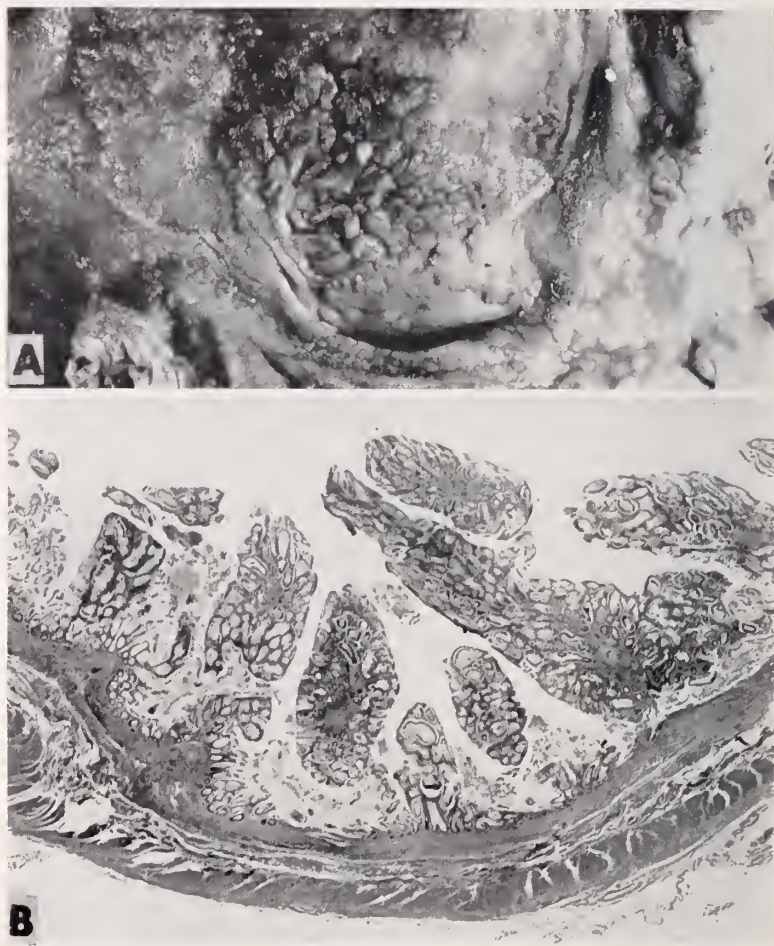


FIG. 6. (Case 4) A. shows multiple adenomatous polypi found in the cecum. B. shows microscopic picture of A. Note presence of dedifferentiated mucous glands.

from multiple polyposis. In the polypi areas of dedifferentiation of mucosal glands were present, proving that they were adenomatous and not inflammatory in nature.

It is well known that in familial polyposis multiple primary carcinomata may develop simultaneously. In one case observed at the Mount Sinai Hospital five grossly recognizable primary carcinomata were found at autopsy. In ordinary carcinoma of the colon the tumor in the colon remains localized although wide-

spread carcinomatous lesions may be found in the abdominal cavity, lymph nodes and liver. Metastasis within the colon develops only by submucous spread. In case 4, described above, the carcinomatous infiltration in the colon was highly suggestive of a multicentric origin, since carcinoma was present diffusely, almost throughout the entire colonic wall. This was certainly different from the pattern

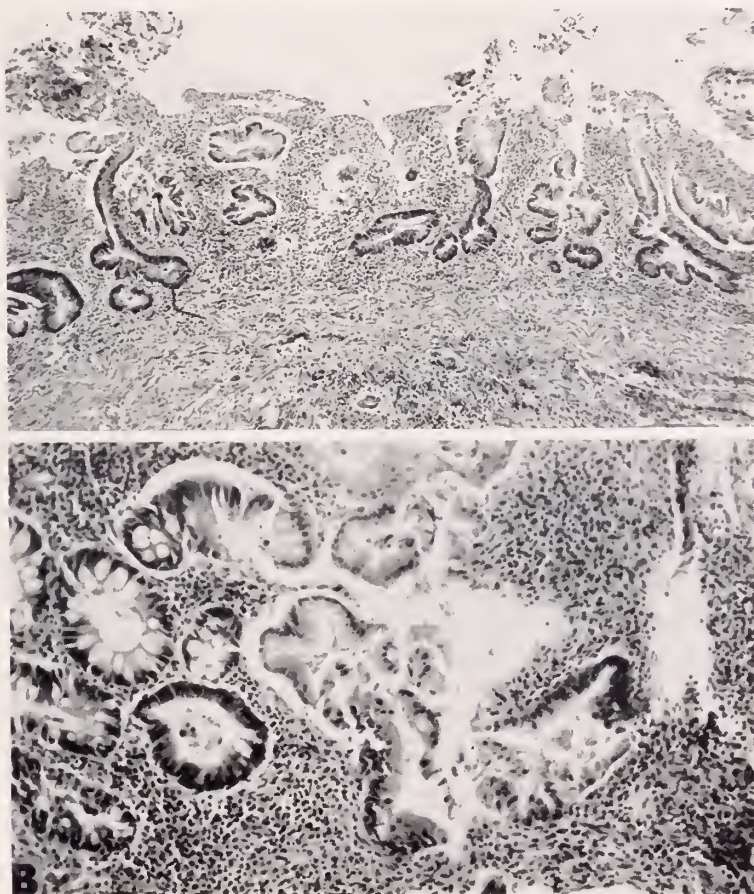


FIG. 7. (Case 4) A. shows irregular glandular structure in healing colitis area. B. shows dedifferentiated glands with early malignant change.

in ordinary carcinoma and suggested malignant degeneration of a familial polyposis.

The definition of familial adenomatosis is an important part of this particular problem. It has always been assumed that familial polyposis is characterized by the presence of innumerable polypi. This concept is too rigid and, therefore, erroneous. Even in the familial type of polyposis the number of polyps is occasionally not excessive. Not the number, but the microscopic type of the polyps determine the tendency to malignant transformation. Unfortunately it can not yet be stated which one of the various types of adenomatous polypi are the ones

which become malignant. But it is certain that the inflammatory polyps as seen in ulcerative colitis do *not* undergo this transformation.

It is also important to note that many adenomatous polypi may be destroyed by secondary ulcerative colitis. In Case 4 (figs. 6 and 7) this assumption seems logical because the colitis started at so early an age.

III. CASES OF CHRONIC ULCERATIVE COLITIS IN WHICH SPORADIC ADENOMATOUS POLYPI ARE FOUND

Among cases of surgically resected chronic ulcerative colitis, one finds sporadic adenomatous polypi in addition to the usual inflammatory polypi. This finding is of importance for the discussion of the incidence of malignancy in cases of chronic ulcerative colitis. Such adenomatous polypi may be responsible for the occurrence of carcinoma in chronic ulcerative colitis.



FIG. 8. (Case 5) shows smooth mucosa of chronic ulcerative colitis and four adenomatous polypi (non-inflammatory polypi).

This is illustrated by a 39 year old male (Case 5, P. 40634), who had symptoms of ulcerative colitis continuously for at least $3\frac{1}{2}$ years before operation. The resected portion of his colon showed severe chronic ulcerative colitis with scattered areas of acute inflammation. Unusual however, was the presence of several polypi which—although pedunculated—were proved by microscopic examination to be adenomatous in nature (fig. 8).

This case then can be considered as an ordinary chronic ulcerative colitis with incidentally co-existing adenomatous polypi, or it can be interpreted as a case of multiple polyposis in which most of the polypi were destroyed by severe ulcerative colitis. A definite decision as to the exact nature of the disease process is difficult since only a part of the colon had been resected surgically, and it is unknown whether in the remaining colon other lesions existed. In any event, attention should be drawn to the fact that in cases of chronic ulcerative colitis adenomatous polypi may be present.

All this is important for the correct evaluation of the following observation, which at first view seems to be a perfect example of the development of a malignancy in a case of chronic ulcerative colitis. In this patient (Case 6) with signs

and symptoms of longstanding ulcerative colitis, an ileosigmoidostomy had been performed many years previously. Later the diseased colon was resected. In the resected specimen (P. 30090), the entire mucosa was atrophic and smooth, and microscopically revealed healed ulcerative colitis. The lining consisted of low colonic mucosa without any inflammatory polypi. Due to the previous ileosigmoidostomy, the colon wall itself had become extremely atrophic and the lumen was markedly narrowed. In the central portion of this resected colon an indurated area 3-4 cm. in length was found, which microscopically proved to be an infiltrating colloid adenocarcinoma (fig. 9).

The question whether this tumor was actually a primary adenocarcinoma cannot be answered with certainty. The specimen was surgically resected and it seems at least possible that the tumor was metastatic to the colon. The absence



FIG. 9. (Case 6). The irregular area of the center portion of atrophic colonic mucosa indicates infiltrating adenocarcinoma. Note smooth atrophic remaining mucosa.

of clinical signs of an extra-colonic primary carcinoma during the two years following operation does not rule out the possibility that the colonic lesion could have been metastatic in nature. It is well known that metastatic carcinomas involving the colon may simulate primary carcinoma. Another possibility which should be considered in this case is the development of a carcinoma in a pre-existing adenomatous polyp.

As shown in Case 5 (fig. 8) adenomatous polypi may coincidentally be found in cases of chronic ulcerative colitis. In multiple polyposis, carcinoma of the colon may sometimes develop in areas of the healed colonic mucosa where no adenomatous polypi but only dedifferentiated mucous glands are present (fig. 5b). It is unlikely that in Case 6 the mucosa of a healed ulcerative colitis, without any dedifferentiation of glands suddenly could have instigated a new growth without a predisposing cause, for tumor formation in a long-standing inflammatory condition must be extremely rare. In discussing the relationship between inflammation and neoplasm, Ewing made the following statement: "The trans-

formation of an inflammatory process to neoplasm is very rare, and a dangerous assumption." At the Mount Sinai Hospital examination of more than 100 specimens of chronically inflamed anal tissue, removed for fistulae or ulcerated hemorrhoids during the past 20 years, revealed only one instance which could be interpreted as very early squamous cell carcinoma.

Thus it is our belief that the carcinoma found in the resected colon of Case 6 originated in a coincidentally existing adenomatous polyp, at least, if the possibility of a metastasis can be ruled out. When one resected specimen of colon shows two different lesions, such as colitis and carcinoma, it is dangerous to draw the conclusion that one may be the cause of the other. At the autopsy table it is not unusual to see two coincidentally existing different lesions which bear no relation to each other.

The following case is such an example: (A-13235) A 22-year old female had had symptoms of colitis for at least 7 years. Necropsy disclosed a severe chronic ulcerative colitis and a carcinoma. This tumor, however, was metastatic in nature. The primary carcinoma was found in the ovary and not in the colon.

Almost without exception familial polyposis and ulcerative colitis are found coexistent at the time of operation or autopsy. Therefore it is interesting to record the following observation where polyposis and carcinoma development came first, the ulcerative colitis later.

This was the 4th admission to Mount Sinai hospital of a 67 year old Russian born, married white male, retired garment worker, admitted for jaundice.

The patient's first two admissions in 1940 were for a two stage resection of a carcinoma of the ascending colon. First an ileotransverse colostomy was performed, followed by a resection of the ascending colon. The pathologic specimen revealed a polypoid carcinoma in the ascending colon with no involved lymph nodes. In the proximal portion of the ascending colon several non-inflammatory benign polyps were found. Following the second operation, the patient remained perfectly well until 1946, when he was readmitted because of an episode of melena (described as black stools and mixed with red blood). At this time sigmoidoscopy and barium enema were negative except for a few diverticula. In 1947 the patient began to complain of diarrhea, having 2-6 stools daily, which ranged from unformed to loose and watery. Only occasionally a few drops of blood were seen at the end of defecation. There was no associated fever, abdominal pain or tenesmus. Barium enemas, done in the OPD in 1950, revealed diffuse changes characteristic of chronic ulcerative colitis involving not only the entire colon from the rectum to the hepatic flexure, but also the distal stump of the ileum at the site of the ileotransverse colostomy and one foot of the afferent loop of the ileum. There were some polypoid changes of the mucosa of the colon. In September 1951, the patient had a tarry stool, dizziness and weakness. Because of the persistence of these symptoms he was hospitalized in a small country hospital, where he received four transfusions of whole blood. These transfusions took place on September 7th, 8th, 10th and 11th. A febrile reaction followed which was treated with penicillin. Two weeks after the last transfusion he had thick, dark brown urine and pale stools, both of which persisted for two additional weeks. At that time (about October 6th, one month following transfusions) he consulted a physician who noted icterus and an enlarged liver. Although the color of the urine became lighter, the jaundice of the sclerae and skin persisted and were still present when on November 15, 1951, about two months after the last transfusion, the patient was readmitted to the Mount Sinai Hospital. Patient's appetite had remained fairly good, although his food capacity was small. His diarrhea persisted with no recurrence of melena, but he had lost 25 pounds in the past several months. Patient noted some itching

in the week prior to admission, but denied fever, chills and sweats. He admitted that his food intake in general was not good and he denied the use of alcoholic beverages. For the month prior to admission, he had also felt transitory sticking pains in the right flank and right lower quadrant. He had complained of arthritis for the past year with pains in the shoulders and knees, for which he had received 60 tablets of cortisone by mouth with some relief of symptoms. He had noted fatty food intolerance for many years with postprandial distention which was relieved by belching and sodium bicarbonate. He admitted occasional pressing substernal pain after meals and on exertion, which was always relieved by rest.

Examination revealed a well developed, but thin and chronically ill appearing elderly white male with marked icterus of skin and sclerae and evidence of marked weight loss and wasting. Temperature, 99.6°; Pulse, 84; Blood pressure, 120/60; Respiration, 18. Liver palms present. Early clubbing of fingers. Some telangiectasis but no frank spider angiomas. No edema. Examination of the eyes revealed in addition to icterus a marked lid lag with poor convergence and scattered yellowish-white retinal exudates. The tongue was smooth and reddened. Examination of the head, skull, eyes, ears, nose and throat was otherwise unremarkable. The trachea was in the midline, the thyroid not palpable, the neck veins flat. There was some generalized glandular enlargement with bilateral axillary, inguinal and femoral firm and discrete nodes 1 to 1.5 cm. in size. Examination of the chest revealed normal findings. The heart was slightly enlarged to the left. There was a soft grade 1 apical systolic murmur. There was a bulging incisional hernia in the RLQ. The liver was enlarged 3 cm. below the right costal margin in the midclavicular line with a firm, smooth, sharp and slightly tender edge. The left lobe felt hard and extended 5 cm. below the xyphoid. There was a firm, blunt spleen tip 2 cm. below the costal margin. No ascites. Some shock tenderness over the RUQ and right lower costal cage. External genitalia unremarkable. Examination of the rectum revealed a slightly enlarged, but symmetrical prostate. On the rectal mucosa on both anterior and posterior walls there were palpable firm, sessile nodules 1 cm. in size. The extremities were unremarkable. All peripheral pulses were patent. There was no edema.

Laboratory Data: Hemoglobin, 9.6 Gm.; Red blood cells, 3.18 million; white blood cells ranging from 4700 to 3150 with 57 segs., 10 non-segs., 31 lymphs., 1 eos., 1 mono. Sedimentation rate, ranging from 65 to 99 mm. per hour. Urinalysis revealed a specific gravity of 1.024, reaction acid, trace of albumin, no sugar, 1-3 plus bile. Urobilinogen 1:8 ranging to 1:80. Microscopic examination negative. BUN, 10 mg. %. NPN, 27 mg. %. FBS, 100 mg. %. T.P., 5.67 Gm. %, albumin, 1.75 Gm. %; globulin, 3.92 Gm. %. Prothrombin time, 17 sec.; control, 11 sec. Bilirubin ranging from 2.3 to 5.4 mg. %. Total cholesterol, 191 to 220 mg. % with 100 mg. % esters. Alkaline phosphatase ranging from 47 to 67 King-Armstrong units. Cephalin flocculation 4 plus. Thymol turbidity ranging from 15 to 24 units. Stool guaiac usually 4 plus. Galactose tolerance test: 2.45 Gm. excreted. After intravenous injection of 0.65 Gm. of sodium benzoate, 0.75 Gm. of hippuric acid were excreted (borderline of normal). Iliac crest bone marrow was unsatisfactory but revealed no tumor cells. Sigmoidoscopy revealed two polyps (sessile) at 2 inches and 8 inches above the anus and a mucosa which bled slightly but did not appear ulcerated. Biopsy (Path 110499) revealed a typical adenomatous polyp (fig. 10),—not an inflammatory one. Biopsy of an inguinal lymph node revealed only a fatty and fibrotic, chronically inflamed lymph node with no evidence of carcinoma (Path. 110488). Blood studies, including bleeding time, clotting time and platelets (260,000) were all normal. Sputum cultures revealed no pathogens. Serum mucoprotein level was elevated to 90 mg. %. Electrocardiogram was normal. X-ray of the chest was normal. Barium enema (x-ray 150215) revealed extensive ulcerative colitis involving the entire large bowel with loss of normal mucosal pattern, narrowing of lumen, irregular contour and numerous, rounded filling defects representing polypoid changes (fig. 11). Similar involvement was seen in both the blind loop of the ileum and a long portion of the afferent loop. Barium meal revealed no definite evidence of esophageal varices, but a deformed duodenal bulb with thickening of folds and a large ulcer crater at the base of the duodenum. There was no abnormality in the proximal small bowel.

Course: The hospital course was characterized by persistence of jaundice which at least chemically increased slightly. Although the stools were usually guaiac positive, after initial transfusion the hemoglobin was maintained. There was persistence of diarrhea with up to six semi-formed stools daily. Patient remained essentially afebrile with occasional unexplained temperature elevations above 100 degrees. In the beginning of the 4th hospital week, despite the increasing jaundice, patient began to complain of pain in the large joints and developed objective changes of swelling and tenderness. Because of the presence of an active duodenal ulcer it was felt that salicylates should be used with caution and he was given enteric coated aspirin tablets, however, without relief. The aspirin induced nausea and vomiting and soon the vomitus became frankly coffee-ground and there was a slight fall in blood pressure. The hematemesis required a blood transfusion.

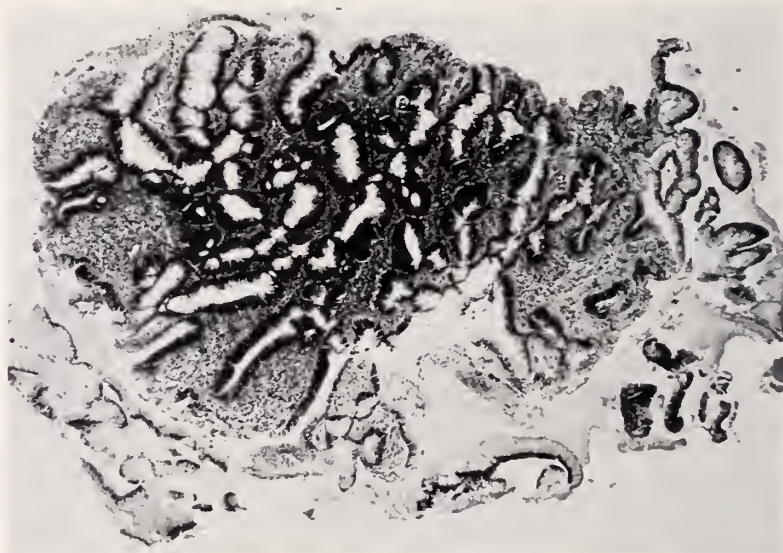


FIG. 10. A biopsy (110499) specimen of rectal polyp shows no evidence of inflammatory polyp, but microscopic structure of adenomatous nature.

It was the clinical impression that the jaundice was hepato-cellular in origin (abnormal liver function tests) superimposed upon a cirrhotic process.

Comment: This case again illustrates the frequency of the development of ulcerative colitis in patients with familial polyposis. In this patient a carcinoma of the colon was removed in 1940 and signs of ulcerative colitis developed in 1946. This sequence of events immediately invoked the suspicion that one underlying condition was responsible for both disorders and that the carcinoma had developed due to degeneration of an adenomatous polyp. In a primary carcinoma of the colon, which has not developed on the basis of malignant degeneration of an adenomatous polyp, ulcerative colitis is extremely rare. Re-examination of the specimen removed in 1940, proved that the clinical impression had been correct. In this case too, it is quite evident that familial polyposis predisposes to the ulcerative inflammation of the colon. If in this patient the ulcerative colitis had developed a few years before 1940, a surgical specimen would again have been

obtained in which carcinoma and ulcerative colitis were coexistent. Only the fortunate circumstance that the polypoid carcinoma developed first, and the ulcerative colitis later, excluded the inflammation as the cause of the malignancy in this patient.



FIG. 11. The colon shows diffuse ulcerative colitis involving the entire large bowel with loss of normal mucosal pattern, narrowing of lumen, irregular contour and numerous, rounded filling defects representing polypi varying in size.

SUMMARY

Although many patients present the clinical combination of chronic ulcerative colitis and carcinoma of the colon, the conclusion that in such cases the carcinoma is secondary to the chronic inflammatory process is not justified. There are many ways in which these two entities may become coexistent. Multiple familial polyposis of the colon frequently leads to malignant changes and often causes a chronic ulcerative colitis. Sometimes this basic pattern is not obvious, either because most of the non-malignant adenomatous polypi have been destroyed by the secondary ulcerative process, or because not too many adenomatous polypi

were originally present. The adenomatous polypi can still be recognized as such since they contain dedifferentiated mucous glands which permits to distinguish them from the inflammatory polypi with low colonic mucosa. Thanks to this histological characteristic, it often may be established that adenomatous polypi are present in a colon in which, at the same time, chronic ulceration and carcinoma are found. Multiple areas of carcinoma in the colon are caused by multicentric malignant degeneration of adenomatous polypi and cannot be metastases from a solitary carcinoma of the colon secondary to ulcerative colitis. In addition it should be emphasized that localized ulcerative colitis frequently develops proximal to a stenosing carcinoma and secondary to it. The fact that adenomatous polypi can be seen in the colon in longstanding chronic ulcerative colitis is important, because these adenomatous polypi actually may be responsible for the carcinoma formation.

One case is reported in which carcinoma of the colon first developed as a result of malignant degeneration of an adenomatous polyp. Five years later ulcerative colitis set in—as is so often the case in adenomatous polyposis of the intestine.

If the ulcerative colitis had developed before the malignant degeneration in this case, it might erroneously have been considered to represent another instance of a carcinoma developing on the basis of a non-specific colitis.

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CORONARY ATHEROSCLEROSIS IN THE YOUNG: CLINICAL AND PATHOLOGIC OBSERVATIONS*

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The concept that atherosclerosis is a disease and not merely the result of wear and tear has received ample support by the experimental and clinical contributions of many workers. Detailed discussion will be found in several reviews and monographs (1-9). In a number of publications from this and other hospitals the metabolic and genetic aspects of atherosclerosis of young age were reported (10-12). The question arose whether these factors are of similar importance in atherosclerosis of old age, or, in other words, whether atherosclerosis of young age differs materially from that seen in old age.

This study presents clinical and pathological observations in fifty persons whose age varied between 27 and 46 years. They died of coronary artery disease and came to autopsy at Mt. Sinai Hospital during the last twenty-two years (1928-1950). For purposes of comparison, a similar group of fifty individuals over the age of sixty was selected from the autopsies of the last few years. In the following presentation the data obtained in both groups will be discussed. number of patients died too soon after admission to obtain satisfactory clinical or laboratory data. However, in the majority, adequate information was available.

YOUNG AGE GROUP

Clinical Observations: This group consisted of 39 males and 11 females. The ages ranged from 27 to 46 (average 41) in both sexes. It should be mentioned at this point that statements concerning age are notoriously unreliable in women; furthermore, many of the foreign-born lacked reliable information concerning their age. For that reason, papers dealing with coronary artery disease in women below 40 have to be taken with reserve. (13). The preponderance of Jewish patients in the hospital population is reflected in this group of which forty-five were Jewish. Information concerning body weight was available in twenty-one males and eight females; the weight ranged from 111 to 220 lbs. (average 152 lbs.) for the former and 131-182 lbs. (average 153 lbs.) for the latter. A tendency to overweight was thus seen in both sexes, especially among the women. Familial occurrence of heart disease was present in thirteen persons out of forty-seven in whom a family history was obtained. The duration of the disease varied from 1 day to 60 months (average 19 months) on the basis of information available in 40 patients; the duration of precordial pain ranged from

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1 day to 60 months (average 17 months); cardiac failure was observed in forty-five individuals during time periods varying from 1 day to 36 months (average 3.6 months). Eight patients were heavy smokers.

Other associated diseases were: arterial hypertension in eight (including two cases of malignant nephrosclerosis), diabetes in 4, syphilis in 3, xanthomatosis and active rheumatic heart disease in 2 instances and 1 instance each of acute glomerulonephritis and thromboangiitis obliterans. The importance of the latter condition will be discussed later. In two instances, coronary occlusion followed a surgical procedure.

Only some of the important clinical data will be presented. Enlargement of the heart was present in 25 out of 42 patients, valvular disease in two. Information concerning blood pressure was available in 43, 8 of whom had hypertension with a range of 130–220 mm. Hg systolic and 90–140 mm. Hg diastolic, average 172 and 111, respectively. Typical electrocardiographic changes were seen in 35 out of 36 patients examined. There was fever up to 106°F; the average of 40 patients was 101.9°. The white blood count was elevated up to 45,000; the average of 37 patients was 18,200. The sedimentation rate was rapid in 10 out of 14 patients. Serum cholesterol determinations (method of Bloor) were done in 17 patients, 6 of whom showed values above 300 mg., five, 250–300 mg. and six, below 250 mg. per 100 ml. The range was 175–960 mg.; the average, 348 mg. per 100 ml.

In three instances, the patients were members of families in which hypercholesteremia was prevalent. In one of them this relationship became apparent many years after the patient's death as may be seen from the following case presentation.

S. D., a 31-year-old man was referred to the hospital because of severe precordial pain. He had experienced pressure in the chest for over a half year. He died shortly after admission to the hospital. Necropsy (P.M. 6837) revealed moderate obesity. The heart weight was 450 grams, the heart muscle was flabby, there was acute myomalacia and myofibrosis with aneurysm formation of the left ventricle; fresh thrombotic occlusion of the right coronary artery and old occlusion of the left anterior descending branch were found. The aorta and its large branches showed advanced atherosclerosis.

The brother of the patient died 10 years later at the age of 37 of coronary thrombosis and a sister, 14 years later, at the age of 43, of the same cause. During her hospitalization, she and the surviving family members were examined for stigmata of hypercholesteremia.* Of the six siblings, four exhibited coronary disease with death in three at 43, 37 and 31 years of age, respectively. All surviving siblings had hypercholesteremia, which was also present in 2 children of one sibling. Thus, the cause of S. D.'s extensive and premature atherosclerosis with fatal outcome at 31 became clarified 14 years later, when the prevalence of hereditary hypercholesteremia was ascertained in the family.

Post Mortem Observations: Of the extensive autopsy studies only those pertaining to the cardiovascular apparatus will be discussed except for an occasional interesting finding in other organs. The heart weight ranged from 230 to 670 Gm. in forty-five instances. It was less than 300 Gm. in two, 300–399 in seventeen, 400–499 in fourteen, 500–599 in seven and over 600 Gm. in five instances. Four of these five hearts had one or two old infarctions with aneurysms;

* The family tree was previously published in this Journal (11a).

the fifth came from a patient with syphilis, acute glomerulonephritis and hypertension.

The site and age of coronary occlusion were as follows: The right artery showed in 24 instances a fresh occlusion and in 6 an old occlusion which in four instances was combined (fresh and old). The descending branch of the left coronary artery was affected in 30 instances by a fresh and in 20 instances by an old occlusion of which 12 were combined. The left circumflex branch was involved in 3 instances by a fresh and once by a combined occlusion. In the majority of the cases the occlusion of the coronary arteries was associated with a fresh thrombosis (40 cases.) In 7 cases, a fresh hemorrhage into an intimal plaque with or without thrombosis was the basis for the occlusion. In the three remaining cases "gross closure," "almost complete occlusion," or "sclerotic occlusion" were the underlying mechanisms. It must be stressed that this observation material was collected during the last 22 years. In the earlier part of this period the concept of fatal coronary insufficiency without thrombotic occlusion and the importance of acute hemorrhage into intimal plaques did not receive adequate attention.

The involvement by atherosclerosis of the aorta and systemic arteries was recorded in 43 instances and graded as minimal 8, moderate 25, severe 10. Although this evaluation was subjected to individual differences of opinion due to the fact that the necropsies were performed by a number of prosectors, the difference between the severe coronary and comparatively moderate or mild systemic (aortic) atherosclerosis was impressive.

Myocardial involvement was recorded in 47 instances. Evidence of acute or subacute myomalacia was present in 13 instances, myofibrosis in 5 and a combination of both in 29.

The microscopic study of the coronary arteries failed to yield distinct qualitative criteria characteristic of this age group. The features of intimal thickening with hyalinization and vascularization, foam cells, necrosis, cholesterol deposits and calcification were found without constant relation to the patient's age, although the impression was gained that the severely distorted arteries were less common in the young group, as was expected. Because of the nature of the pathological material which was collected over a period of over 2 decades the histological studies were, as a rule, limited to hematoxylin eosin sections. Only occasionally could elastica and van Gieson stained sections be used. Studies of lipid material, lime salts and chromotropic substance, etc., were therefore omitted.

An interesting observation which was made in the youngest individual in this group, a man of 27, concerned a stenosing process of a coronary artery with superimposed thrombosis and accompanied by an acute arteritis.

I. S. (Adm. No. 447634) was admitted to the hospital because of sudden onset of severe substernal pain accompanied by cold sweat, weakness and vomiting. The pain was partially relieved by a hypodermic injection. He had had scarlet fever in childhood and was told he had a murmur seven years ago. He smoked 20 cigarettes daily.

Physical examination revealed an apprehensive, pale young man with soft, thud-like

heart sounds and a soft systolic murmur, temperature 97, pulse-rate 128, blood-pressure 130 systolic, 90 diastolic. There was evidence of acute tonsillitis. Laboratory findings: Hgb. 105%, red blood cells 5.9 million, white blood cells, 29,200. Blood Wassermann reaction, negative; blood sugar 105 mg. per 100 ml., serum cholesterol 250 mg. per 100 ml., blood urea nitrogen, 23 mg. per 100 ml. The electrocardiogram revealed changes characteristic of acute anterior wall infarction.

The course seemed at first satisfactory. The blood pressure was 112 systolic and 84 diastolic on the second day, the temperature 102. Death occurred suddenly on the third day.

Autopsy (*11306) revealed a well developed and nourished body. The heart weight was 350 grams. The myocardium of the entire anterior wall of the left ventricle, of the anterior half of the septum and of the apical portion of the posterior wall showed a yellowish-grey discoloration best seen on cut surface with extensive irregular bluish-red areas. Similar changes were also present in the left anterior papillary muscle. A small, red, mural thrombus was seen in the apex of the left ventricle. The coronary ostia were patent. The coronary arteries disclosed a mild degree of atherosclerosis. The left anterior descending branch was occluded by a red thrombus which filled the narrowed lumen for a distance of 2.5 cm., beginning 1 cm. below the ostium. The aorta showed a moderate degree of atherosclerosis in the ascending and lower lumbar segment. The remainder of the autopsy revealed acute pulmonary edema and congestion of the abdominal viscera.

Microscopic examination of the myocardium showed acute necrosis. The cross-section of the left anterior descending coronary artery disclosed a fresh thrombosis occluding an already greatly and eccentrically narrowed vessel. The most impressive finding was the presence of large numbers of polymorphonuclear leucocytes in the thickened, edematous intima and in the media. A stain for bacteria was negative. Near the lumen there was a deposit of homogeneous eosinophilic material resembling fibrin on which, in turn, a fresh thrombus became attached. (See Figs. 1 and 2). Elastic stains disclosed splitting of the internal elastic membrane underneath the thickest part of the intima. The outer coats of the artery were not remarkable except for the above mentioned acute inflammation of the media and conspicuous hyalinization of the adventitia, particularly underneath the intimal plaque. A section of two somewhat smaller epicardial coronary branches likewise showed acute inflammation of eccentrically stenosed arteries and fresh thrombosis. Sections of systemic arteries (splenic, hepatic, renal) showed no significant changes. A small subcapsular chromophobe adenoma was seen in the anterior lobe of the pituitary. There was evidence of chronic and acute antral gastritis. The tonsils could not be examined due to limitations of the autopsy permission.

Comment: The youngest individual, a 27-year old man, who died of acute coronary occlusion presented only mild atherosclerotic lesions of coronary arteries outside the occluded segment and moderate lesions of the aorta. There was, however, evidence of a stenosing coronary lesion accompanied by features of acute arteritis and thrombosis. ("Arteriitis stenosans coronariae" of von Albertini (14).)

OLD AGE GROUP

Clinical Observations: This group was used as a control group and consisted of 29 males and 21 females. The age range was 60 to 76 years for the males (average 67) and 60 to 83 years for the females (average 69).

There is a preponderance of Jewish patients, amounting to 41 in this group. Information concerning weight was obtained in 31 instances, 18 males and 13 females; the weight ranged from 120 to 185 lbs., average 151 lbs. in the former and 85 to 184 lbs., average 134 in the latter. Tendency to overweight was less pronounced in the females. Familial occurrence of heart disease was present only

in one and perhaps in one additional case out of 50. Based on information obtained in 39 patients the duration of the disease ranged from 2 days to 16 years, average close to 4 years (46.1 months); precordial pain as the leading symptom

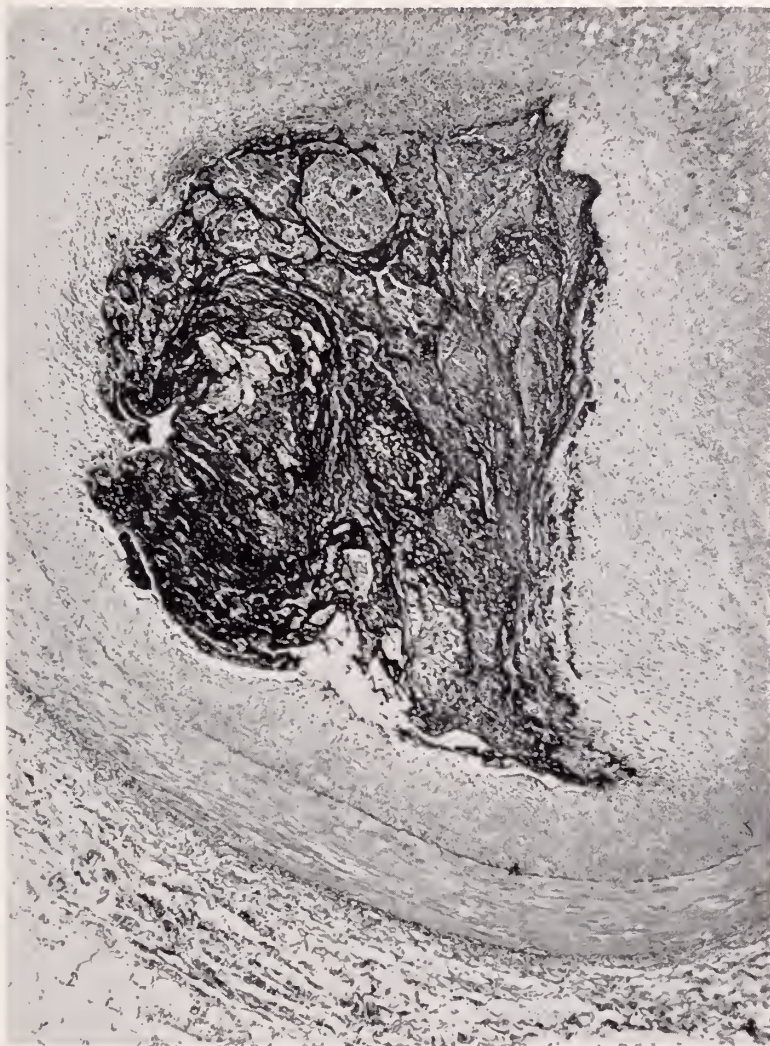


FIG. 1. Left coronary artery of 27 year old man. The clot is firmly attached throughout most of its circumference except for the portion opposite the relatively thin part of the intima. The slender, dark band parallel to the right margin of the picture is "fibrinoid." (Mallory's phosphotungstic acid hematoxylin.)

was observed from 1 day to 16 years with an average of about $3\frac{1}{2}$ years (44.8 months); in 10 additional patients there was no history of previous precordial pain. Data concerning duration of cardiac failure were obtained in 29 patients; it ranged from 2 days to 16 years, the average being about 2.5 years (30.3 months). None of the patients considered himself a heavy smoker.

There was a high incidence of hypertension and diabetes. Hypertension was present in 28, including one case of polycythemia. This figure was probably considerably higher, since some of the patients who had been admitted in shock

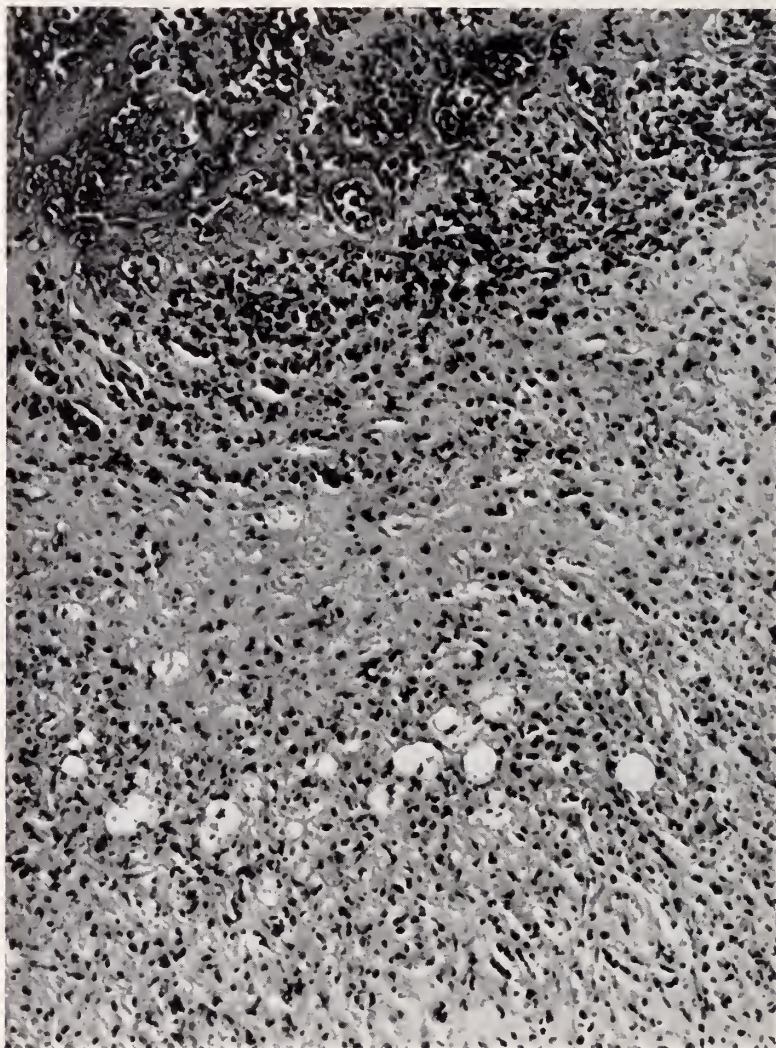


FIG. 2. There are many inflammatory cells in the thickened intima. (Hematoxylin, Eosin)

might have been hypertensives without having known it. There were 14 patients with diabetes; of these 4 were admitted in diabetic acidosis and developed clinical evidence of coronary occlusion while in the hospital and 3 had an associated Kimmelstiel-Wilson syndrome. Latent syphilis was found in one instance only. Corneal arcus was recorded in 8 patients. Rheumatic heart disease was reported in 3 patients of whom one had severe kyphoscoliosis with cor pulmonale and

hypertensive heart disease. Xanthomatosis was seen in one patient only. In six cases coronary occlusion developed as a post-operative complication. Four patients had peptic ulcers (2 duodenum, 1 stomach, 1 esophagus). Anginal pain started during the post-operative course in two instances. Six patients had signs and symptoms of cerebral hemorrhage, only one of which was recent.

Enlargement of the heart was present in 28 instances out of 31. Valvular disease was recorded only once. In the 28 hypertensive patients the systolic pressure varied from 120 to 240 mm. Hg and the diastolic, from 74 to 150 mm. Hg. The average was 180 and 105 respectively. Typical electrocardiographic findings of acute myocardial infarction were observed in 35 out of 45 instances. The highest peak temperature was 105.6°F, the lowest, 97. The average peak temperature in 45 patients was 101.5. The highest white blood count was 39,000, the lowest, 4,600 and the average in 39 patients was 15,400. Out of 17 patients 13 had a rapid sedimentation rate. Serum cholesterol was determined in 18 instances and ranged from 161 to 410 mg. per 100 ml., average 275 mg. In 7 patients the level was over 300 mg., in four, 250 to 300 and in 7, under 250 mg. per 100 ml.

Post Mortem Observations: The findings, again, will be confined to the cardiovascular system. The heart weight ranged in this group from 280 to 700 Gm. This information was available in all 50 cases. A heart weight of less than 300 grams was encountered only once, of 300-399 Gm. 25 times, of 400-499 gm. 15 times, of 500-599 Gm. 6 times, over 600 Gm. 3 times. Two of these three hearts came from hypertensives with prolonged failure, while the third showed a cardiac aneurysm.

The location and age of the coronary artery occlusion was as follows: There was in 18 instances a fresh and in 7 an old occlusion of the right coronary artery which in 3 instances was combined (fresh and old). The descending branch of the left coronary artery showed fresh occlusion in 20 and old occlusion in 12 instances of which 2 were combined. The left circumflex branch was affected in 11 instances by a fresh occlusion and in 4 by an old occlusion.

In 41 instances, the fresh occlusion resulted from thrombosis. Of the remaining 9 instances, six revealed fresh hemorrhages into intimal plaques with or without thrombosis; finally, in 3 instances, no thrombosis or intramural hemorrhage was found microscopically, but "almost complete occlusion by atheroma," "calcific occlusion of right with severe narrowing of left coronary" and "severest stenosis of all three coronary branches by atherosclerosis" were noted.

In addition to coronary atherosclerosis there was involvement of the aorta and the systemic arteries in 43 instances in which 34 had severe, 8 moderate and 1 minimal involvement.

Myocardial damage was noted in 49 instances. Acute and/or subacute myomalacia was present in 16 instances, myofibrosis in 5, myomalacia plus fibrosis in 28.

DISCUSSION

A comparative study was made of a young group (ages 27 to 46) and an old group (ages 60 to 83) comprising 50 persons each with fatal coronary artery

disease. The most important findings in both groups are presented in tables 1 and 2.

The younger group is characterized by an increased familial occurrence of

TABLE 1
Clinical and laboratory findings

	YOUNG AGE GROUP	OLD AGE GROUP
<i>Sex</i>		
Males.....	39	29
Females.....	11	21
<i>Average age</i>	Males, 41; females, 41	Males, 67; Fem., 69
<i>Range of age</i>	Males, 27-46; females, 27-45	Males, 60-76; Fem., 60-83
<i>Extraction</i>		
Jewish.....	45	41
Non-Jewish.....	5	9
<i>Body wt.</i>		
Males.....	111-220 lbs; aver. 152(1) (i.a. in 21)	122-185 lbs.; aver. 151 (i.a. in 18)
Females.....	131-182 lbs.; aver. 153 (i.a. in 8)	85-184 lbs.; aver. 134 (i.a. in 13)
<i>Familial occurrence of heart disease</i>	13 (i.a. in 47)	1(+1?) (i.a. in 50)
<i>Average duration of disease in months</i>	19.2; range 0.03-60 (i.a. in 40)	46.1; range 0.06-192 (i.a. in 39)
<i>Average duration of precordial pain, ms.</i>	16.8; range 0.03-60 (i.a. in 40)	44.8; range 0.03-192 (i.a. in 38); (an add'l. 10 had no pain).
<i>Average duration of cardiac failure, ms.</i>	3.6; range 0.03-36 (i.a. in 45)	30.3; range 0.06-192 (i.a. in 29)
<i>Heavy smoking</i>	8	None
<i>Known arter. hypertension</i>	8	28 (incl. 1 with polycythemia)
<i>Lues</i>	3	1
<i>Diabetes</i>	4	14 (2)
<i>Xanthomatosis</i>	2	1
<i>Corneal arcus (3)</i>	0	8
<i>Glomerulonephritis</i>	1 (acute)	0
<i>Thromboangiitis obliterans</i>	1	0
<i>Rheumatic heart disease</i>	2 (active)	3 (4)
<i>Malignant nephrosclerosis</i>	2	0
<i>Post-operative death caused by cor. occlus</i>	2	6
<i>Peptic ulcer</i>	0	4 (5)
<i>Cerebral hemorrhage</i>	0	6 (6)
<i>Precordial pain started after operation</i>	0	2
<i>Enlarged heart, clinically</i>	25 (+2?) (i.a. in 42)	28 (i.a. in 31)
<i>Valvular disease</i>	2 (+1?)	1 (+1?)

TABLE 1—*Continued*

	YOUNG AGE GROUP	OLD AGE GROUP
<i>Hypertension</i>		
Incidence	8 (i.a. in 43)	28 (i.a. in 48)
Average, systolic	172; range 130-220	180; range 122-240
Average, diastolic	111; range 90-140	105; range 74-150
<i>Temperature (peaks)</i>		
Highest	106	105.6
Lowest	99.2	97
Average	101.9 (i.a. in 40)	101.5 (i.a. in 45)
<i>Typical ECG</i>	35 (i.a. in 36)	35 (+7?) (i.a. in 45)
<i>White Blood count</i>		
Highest	45,000	39,000
Lowest	5,000	4,600
Average	18,200 (i.a. in 37)	15,400 (i.a. in 39)
<i>Rapid sedimentation</i>	10 (+2?) (i.a. in 14)	13 (+1?) (i.a. in 17)
<i>Serum cholesterol in mgs. per</i>		
100 ml.	(i.a. in 18)	(i.a. in 18)
Over 300	6	7
250-300	6	4
Below 250	6	7
Average	348; range 175-960	275; range 161-410

(1) i.a.; information available.

(2) This figure includes 4 patients who were admitted in diabetic acidosis and developed coronary occlusion in the hospital and 3 with the Kimmelstiel-Wilson lesion.

(3) These figures represent a minimum, as reliable information re arcus was lacking in most patients.

(4) One patient had in addition marked kyphoskoliosis, cor pulmonale and hypertensive heart disease.

(5) Two of these were deaths during the postoperative course.

(6) One of these was fresh.

heart disease; a shorter clinical history and shorter average duration of anginal pain and cardiac failure; a greater preponderance of men; a greater preponderance of overweight women; a high incidence of heavy smokers; a significantly lower incidence of hypertension and diabetes (one-fourth to one-third of that found in the older group); and higher levels of serum cholesterol (average, 348 vs. 275 mg. per 100 ml.)

The clinical findings of the young group are as a whole in good agreement with the extensive literature on this subject. The tendency towards heart disease in family members of young patients with coronary artery disease and the great preponderance of men has been stressed by many workers (10, 16, 17, 18, 19). This preponderance is also reflected in cases of sudden death due to coronary artery disease (15).

The factor of overweight and body build which is evident in our group, especially among the women, has been repeatedly discussed (20). It is of interest, however, that in an extensive series consisting of young soldiers of World War II no great importance was attached to the factor of obesity (17, 21).

Regarding the abuse of tobacco found frequently in the young series, it is interesting to note that some authors in the field (22, 23, 24) were impressed by the incidence of heavy smokers, while others (1, 17, 25) reported equivocal figures. The low incidence of hypertension and diabetes is well recognized since both diseases increase in frequency with advancing age.

Evidence seems to indicate that the cholesterol level of the serum and of the tissues (10b) and perhaps the relationship between cholesterol and phospholipids

TABLE 2
Post-mortem findings

	YOUNG AGE GROUP	OLD AGE GROUP
<i>Heart weight (in Gms.)</i>	(i.a. in 45)	(i.a. in 50)
Below 300	2	1
300-399	17	25
400-499	14	15
500-599	7	6
Over 600	5	3
<i>Site of coronary occlusion</i>		
Right coron. artery		
Fresh occlusion	24	18
Old occlusion	6 (incl. 4, fresh and old)	7 (incl. 3, fresh and old)
Left desc. branch		
Fresh occlusion	30	20
Old occlusion	20 (incl. 12, fresh and old)	12 (incl. 2, fresh and old)
Left circumflex		
Fresh occlusion	3	11
Old occlusion	1 (fresh and old)	4
<i>Involvement of aorta and systemic arteries</i>	(i.a. in 43)	(i.a. in 43)
Severe	10	34
Moderate	27	8
Minimal	8	1
<i>Involvement of myocardium</i>		
Acute and subacute	(i.a. in 47)	(i.a. in 49)
Myomalacia	13	16
Myofibrosis	5	5
Myomalacia plus myofibrosis	29	28

(26-28) and the particle size of the lipids and lipoproteins (29, 29a, 29b) may be significant factors in the development of experimental as well as human atherosclerosis. Independently from these recent biochemical studies conducted in this country, continental pathologists have stressed lately the role of protein-lipid deposits in the arterial intima in the genesis of atherosclerosis (30, 30a, 31b, 32, 32a).

Our study revealed a higher incidence of familial heart disease and hypercholesteremia in the young age group which may indicate that factors of deranged lipid metabolism are of greater importance in coronary atherosclerosis

in younger people. This is in agreement with previous observations of others (11, 33, 34, 35).

The pathological features of the younger hospitalized group were as follows: A greater occurrence of extreme heart weights (500 gm and more) despite the higher incidence of hypertension in the older group. This finding recalls some previous observations (36) and may be explained by the greater power of regeneration of the myocardium in the young (37).

The differences between the two age groups in the microscopic structure of the coronary arteries were less clear-cut, although the younger group had a greater tendency to fibrous intimal proliferation, while the older patients had more atheroma and calcification, which is in agreement with the findings of other authors (5a, 24, 38). In a number of individuals in both groups the coronary artery occlusion did not result from thrombosis or intimal hemorrhage. It is of interest in this connection that several authors recorded a very high incidence of non-thrombotic fatal coronary artery disease in young individuals (15, 17, 23, 24, 39a, 40a, 40b). In certain instances only serial sections of the greatly narrowed portion of the coronary artery will reveal the presence of minute occluding thrombi (40).

The youngest patient of the group, a man of 27, revealed a segmental coronary artery lesion with the features of the acute phase of "arteritis stenosans coronariae." Only mild atherosclerosis was found in the remainder of the coronary tree and moderate sclerosis of the aorta.

The concept of arteritis as a cause of human coronary atherosclerosis is not new. It was supported by numerous authors (41, 42, 43, 44, 45), and was recently revived in a modified form by von Albertini (14). This author separates the primary form of arteriosclerosis from a secondary form in which the intima is thickened by episodes of repeated inflammation. This process is better demonstrated in younger people because of the absence of severe degenerative arterial changes. Von Albertini has gathered evidence for the identity of stenosing coronary arteritis with thrombo-angiitis obliterans (Buerger's disease). Repeated attacks of coronary arteritis lead to renewed intimal deposits of fibrin, thus causing narrowing of the lumen which eventually interferes with the blood supply, or leads to complete occlusion by superimposed thrombus. The rapid disappearance of the polymorphonuclear infiltrate in the arterial wall explains the comparative rarity of the full-blown acute lesion of coronary arteritis.

The chronic phases of coronary arteritis of this type characterized by intimal "fibrinoid" deposits with or without residual cellular infiltration (lymphocytes and plasma cells, sometimes in all three arterial coats) are more common and have been depicted by various authors, although with different interpretations.

The end stage of this stenosing arteritis, provided the patient survived the episodes of acute recurrence, is morphologically indistinguishable from the genuine or primary form of atherosclerosis and is characterized by deposits of hyaline, lipids and lime salts with accompanying distortion of the artery.

This study, then, briefly summarizes the somewhat neglected aspect of inflam-

matory factors in the genesis of atherosclerosis, especially of segmental coronary atherosclerosis in the young.*

SUMMARY

Clinical and pathological features of fatal coronary atherosclerosis in 50 persons, ranging in age from 27 to 46 years, were compared with those of an old age group (50 persons aged 60 to 83 years). The young group was characterized by a frequent familial occurrence of heart disease, shorter duration of anginal pain and circulatory failure, a greater preponderance of males with a high incidence of heavy smokers, a considerably lower occurrence of hypertension and diabetes and higher levels of serum cholesterol.

The pathological features of fatal coronary atherosclerosis in the hospitalized young group were a greater occurrence of extremely heavy hearts (despite the high incidence of hypertension in the older group), disproportion between the severe coronary and mild systemic atherosclerosis, greater tendency to fibrous intimal proliferation and a lesser degree of atheroma and calcification. Special emphasis is placed on the occurrence of a stenosing coronary arteritis in the youngest individual of this group. The somewhat neglected aspects of inflammatory factors in coronary atherosclerosis in the young are briefly discussed.

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* A study of an additional group of 25 individuals between the ages of 24 to 40 will be presented elsewhere (46).

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PROBLEMS IN THE MANAGEMENT OF REFRACTORY HEART FAILURE*

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Intractable heart failure denotes that a patient with myocardial insufficiency has become refractory to all of the known treatments for this condition. If this were literally so, there would be no purpose to this presentation. In practice, however, there is always the hope that the heart failure appears intractable only because of some oversight or incompleteness of diagnosis or some inadequacy or error in treatment. Therefore, when we are confronted with so-called intractable heart failure, it is desirable that we make a systematic review of the case with respect to the following questions: 1. Is the diagnosis of heart failure accurate? 2. Is there a remediable contributory or precipitating factor? 3. Is the basic cardiac disease curable? 4. Is the treatment of the heart failure itself adequate? 5. Has improper or exaggerated treatment caused therapeutic unresponsiveness?

Is the Diagnosis of Congestive Heart Failure Accurate?

No attempt will be made to list all the possible problems in the differential diagnosis of congestive heart failure. However, it should be noted that the diagnosis of heart failure is based on a clinical syndrome characterized chiefly by dyspnea and its variants, and by subcutaneous edema, serous effusions and venous engorgement. Therefore it is necessary to exclude the multiple diseases which can produce these symptoms. Pulmonary disease, carcinomatosis, chronic gastrointestinal bleeding with anemia due to benign or malignant lesions, hepatic and renal disease among others should be carefully considered as possible causes of dyspnea or anasarca attributed to congestive heart failure. In addition to various clinical and laboratory examinations, determinations of the circulation time and of the venous pressure in the upper and lower extremities, simple bedside procedures, are often helpful in distinguishing these diseases from congestive heart failure.

Remediable Factors Responsible for Heart Failure

The outlook for congestive heart failure is exceedingly more favorable if a remediable contributory or precipitating cause can be found, than if the heart failure is the consequence of progressive myocardial dysfunction without any apparent precipitating cause. A systematic search should therefore be made for possible factors responsible for precipitating congestive heart failure or for rendering it intractable to treatment. Among the factors which are susceptible of elimination or amelioration and which can account for the refractoriness of heart failure are the following: (1) Hyperthyroidism. (2) Beriberi. (3) Anemia. (4)

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Arteriovenous fistula. (5) Arrhythmia with tachycardia. (6) Rheumatic fever. (7) Bacterial endocarditis. (8) Pulmonary embolism. (9) Hypertension. (10) Hepatic cirrhosis.

These conditions are not always apparent and may be easily overlooked unless a special effort is made to seek their presence. Hyperthyroidism is particularly important because its diagnosis and cure leads to a brilliant control of the heart failure; on the other hand, its oversight prevents the alleviation of heart failure despite the most vigorous use of all the conventional methods of treatment. Oversight is usually due to the fact that the classic features of hyperthyroidism are often absent in patients with heart failure and that dyspnea may interfere with determination and interpretation of the basal metabolic rate. The measurement of the serum precipitable iodine, or the determination of the radioiodine excretion or its thyroid uptake or the protein-bound radioactive iodine in the blood after the patient has been given a tracer dose of I^{131} will almost always afford an accurate diagnosis as to the presence or absence of hyperthyroidism. If these technical procedures are not readily available, or the results are equivocal in a patient with tachycardia, weight loss, normal or rapid circulation time in the presence of heart failure, or auricular fibrillation with rapid ventricular rate not readily controlled by digitalis, then a therapeutic trial with Lugol's solution should be undertaken, or if this is indefinite, propylthiouracil should be administered.

The next four conditions on the list will not be discussed in detail. The control of the manifestations of heart failure will be incomplete or unsatisfactory unless a vitamin B deficiency is corrected by the use of thiamine chloride and adequate protein intake, or unless severe anemia is corrected by the cautious administration of blood and the elimination of the cause of the anemia, or unless the arteriovenous fistula is corrected surgically, or a tachycardia associated with arrhythmia is slowed with the aid of digitalis, quinidine or other measures.

Active rheumatic fever is a not infrequent cause for intractable heart failure. However, this does not represent a readily remediable factor. Its control may be facilitated, however, by the use of ACTH and cortisone, after which the responsiveness of the heart failure to conventional agents is much more satisfactory.

Bacterial endocarditis is occasionally both the cause of the appearance of congestive heart failure and the reason for its intractable nature. Bacterial endocarditis is especially apt to be overlooked if heart failure is already present, at the time that the patient is first observed or at the time that the diagnosis is first entertained. If the infection is eradicated by antibiotic treatment, the heart failure may be readily controlled. Unfortunately, the development of heart failure often denotes the presence of prolonged and deep-seated infection which can no longer be eradicated, or valvular and myocardial damage may be so extensive that progressive heart failure ensues despite cure of the infection.

Pulmonary embolism is one of the commoner causes for the development and persistence of heart failure and its lack of responsiveness to treatment. The diagnosis is often overlooked because its symptoms may be minimal or masked by those of heart failure. Treatment is often unsatisfactory, but the administration

of anticoagulants may be effective. When pulmonary emboli appear to arise from thrombi in the legs, and if they recur despite the use of anticoagulants, ligation of the veins in the thighs or of the inferior vena cava may have to be undertaken. In a few instances which we have observed venous ligation has had a dramatic effect in permitting control of previously intractable heart failure. When pulmonary embolism is associated with auricular fibrillation and may be secondary to thrombi in the right atrium, a trial with quinidine in an effort to restore regular sinus rhythm may be indicated.

Hypertension may be regarded as the underlying, or as a contributory cause of congestive heart failure. When a diagnosis of pheochromocytoma can be made, heart failure due largely or entirely to the hypertension can be cured by removing the adrenal medullary tumor. In cases of malignant hypertension complicated by heart failure, the use of sympathectomy or extremely low sodium intake may be effective in the control of the cardiac insufficiency.

Cirrhosis of the liver, of the Laennec type, may be associated with congestive heart failure and may be responsible for its refractory nature. Although the results of treatment are not always convincing, there is sufficient evidence to justify the use of a high vitamin B, high protein and high caloric diet in these cases. This presents a difficult test of dietary ingenuity because the use of high protein diets usually necessitates the use of more than minimal sodium intake.

Treatment of Basic Cardiac Disease

When none of these contributory causes can be found, or if the contributory cause cannot be eliminated, consideration must be given to a more direct attack on the basic underlying cardiac disease which is responsible for congestive heart failure. This usually denotes the use of a surgical operation: The following conditions are among those for which surgical correction may be considered: (1) Constrictive pericarditis. (2) Mitral stenosis. (3) Congenital cardiac lesions: (a) patent ductus arteriosus; (b) coarctation of aorta; (c) pulmonic stenosis; (d) septal defects.

Constrictive pericarditis usually presents itself as intractable heart failure. Successful control of the manifestation of constrictive pericarditis requires the surgical release of the heart from its encasing indistensible membrane. Sometimes a clinical diagnosis of constrictive pericarditis cannot be made with assurance and an exploratory thoracotomy must be performed. The treatment of mitral stenosis by surgical enlargement of the tight mitral orifice marks an important milestone in the treatment of cardiac disease because this therapeutic procedure applies to a much more frequent cardiac ailment than those for which other surgical procedures have hitherto been successful. The indications for surgical treatment of mitral stenosis are not yet clearly defined. While the possibility of correcting the causative tight mitral stenosis by commissurotomy or digital fracture of the rigid cusps is mentioned here as a means of controlling refractory heart failure, it is important to emphasize that complications of the operation are much more frequent and the outlook less promising if correction of the lesion is delayed to the stage of intractable heart failure.

The surgical correction of the various congenital cardiac lesions can only be mentioned. As with mitral stenosis, it should be stressed that these congenital lesions should be corrected before rather than after the appearance of intractable heart failure.

The most common underlying cause of congestive heart failure today, namely arteriosclerotic heart disease and its major complication, coronary occlusion, are not directly susceptible to treatment. However, attempts are being made to increase the oxygenated blood supply to the heart, as in the method of Beck, who anastomoses a branch of the aorta with the coronary sinus by means of a vascular graft.

THERAPY OF HEART FAILURE

Having verified that the patient with apparently refractory heart failure is actually suffering from heart failure, that there is no remediable precipitating or contributory factor, and that there is no underlying basic cardiac disease which can be corrected surgically, it is necessary to determine whether the heart failure can be alleviated by a more perfect application of the conventional measures employed in its treatment. It is therefore essential that we systematically review the following measures: (1) The degree of restriction of activity. (2) Digitalization. (3) The degree of restriction of sodium intake. (4) The frequency and type of diuretic employed. (5) The study of blood electrolyte patterns to determine whether they are responsible for therapeutic ineffectiveness.

Restriction of Activity

The importance of rest requires no emphasis. Attention may be called, however, to two points: First, the frequency with which patients with heart failure apparently refractory to treatment respond as soon as they are hospitalized. Often this occurs without any obvious difference, or before any change, in diet, digitalization or use of diuretics. In such cases it appears that the improvement is due essentially to a more conscientious and stricter limitation of activity than at home. In this connection it is well to mention that there is evidence that the tendency to sodium-water retention and edema formation is promoted by activity and conversely that the excretion of sodium and water in response to mercurial diuretics is enhanced by rest, and more specifically by the recumbent as contrasted with the upright position. The second point to be noted in connection with rest is the recent tendency to stress the *dangers* of bed rest. While this emphasis is certainly valid, when interpreted with good sense and moderation, it should not be permitted to lead to a rejection of the well-established advantages of bed rest in heart failure. In most patients with heart failure, complete bed rest may be dangerous as well as unnecessary; in those cases in which heart failure is refractory, therapeutic responsiveness may be unsatisfactory unless the patient is put to bed and kept there until his circulatory status improves. Nothing in these comments about bed rest should be interpreted to mean that the patient may not or should not be allowed to sit up or be propped up sufficiently to control orthopnea; neither should they be interpreted as a prohibition against the

use of a bedside commode or even a nearby bathroom once or twice a day if necessary.

Proper Digitalization

Inadequate or excessive digitalization is only occasionally responsible for intractable heart failure. Severe vomiting and diarrhea may cause electrolyte disturbances which may impair responsiveness to treatment of heart failure. Occasionally we have known patients who have not taken the necessary prescribed doses of digitalis because of the fear of recurrence of these unpleasant gastrointestinal symptoms. Sometimes the clinical symptoms attributed to intractable heart failure or electrolyte disturbances are actually due to digitalis toxicity. Digitalis dosage with the new glycosides as with the whole leaf preparations, must be individualized and the clinical response carefully observed.

Degree of Restriction of Sodium Intake

Seemingly refractory heart failure may respond when the restriction of sodium intake is intensified. While many patients with congestive heart failure can be satisfactorily controlled by omitting salt from their cooking and at the table in addition to avoiding obviously salted uncooked foods (2 to 4 gm. of sodium chloride daily), those with intractable heart failure must be more stringently restricted. Some of these patients will continue to retain sodium, i.e., they will have a positive sodium-water balance unless their sodium chloride intake is reduced to 1 gm. daily, and some must ingest not more than 0.5 gm. daily. Many opportunities for dietary error as well as the impalatability of such extremely low sodium diets explain the therapeutic failures due to inadequate sodium restriction. The knowledge of the relatively high sodium content of such common foods as bread, milk, meats, eggs, and canned vegetables, even when no salt is added, is now widely disseminated. The commercial availability of salt-free or salt-poor bread and milk has been helpful and there is a promise of prepared salt-poor meats. Impalatability of the very low-sodium diets is still a serious difficulty. This may be solved in some patients by permitting a diet containing 3 to 4 gm. of sodium chloride daily, and by administering at meals cation resins of the ammonium or hydrogen cycle. If each gram of resin is capable of carrying with it 1 m.Eq. of sodium, then the commonly recommended 45 Gm. daily of resin may eliminate 45 milliequivalents of sodium (2.6 Gm. sodium chloride). If the patient is on a diet containing 3 Gm. of sodium chloride daily, the resin would permit an absorption of only 7 m.Eq. of sodium or less than 0.5 Gm. of sodium chloride; if the patient is on a diet of 4 Gm. of sodium chloride daily, less than 1.5 Gm. of sodium chloride would be absorbed. Resins will become of greater value in the treatment of intractable heart failure as they become less expensive, more palatable and more efficient.

In contrast with the trend to more stringent restriction of sodium intake in patients with refractory heart failure, the former policy of restriction of fluid intake has been abandoned. In fact there is evidence that a more effective renal diuresis will be obtained with water intakes of 2 or 3 liters daily than with lesser quantities.

Diuretics

Ammonium chloride is mentioned because of three possible effects: 1) It may be used intermittently to enhance the therapeutic effect of the mercurial diuretics. 2) It may intensify certain electrolyte disturbances associated with mercurial diuretics, notably potassium depletion. 3) When administered for long periods without interruption it may cause clinically significant acidosis and the resulting distressing hyperpnea may be misinterpreted as evidence of intractable heart failure.

Apparently intractable heart failure may sometimes be alleviated by more frequent administration of mercurial diuretics. On the other hand, unsatisfactory control of the symptoms of heart failure frequently leads to progressively more frequent administration of these drugs. Danger in the use of mercurials often arises when a satisfactory diuresis no longer follows exhibition of these drugs despite the persistence of frank signs of congestive heart failure. The term mercury fastness is sometimes applied to this state. A number of measures may be utilized in an effort to restore responsiveness to the mercurial diuretics. Bed rest has already been mentioned. Ammonium chloride in doses of 6 to 9 gm. daily may be given for three days prior to the injection of the mercurial. When this is ineffective, 0.5 Gm. aminophylline administered very slowly about an hour or two after the mercurial may serve to potentiate its diuretic activity. It has been noted that in the presence of hyponatremia, that is, low plasma sodium, the response to mercurial diuretics is inhibited. This has been attributed to hyponatremia, and consequent reduction in glomerular filtration, or to consequent adrenal cortical stimulation with increased tubular reabsorption of sodium. These considerations have led to the recommendation that hypertonic sodium chloride be given to increase the plasma sodium in the hope that the mercurial diuretics will then resume their effectiveness. Although the administration of hypertonic sodium chloride to patients with congestive heart failure and hyponatremia is usually surprisingly well tolerated, it is often difficult to increase the plasma sodium concentration to normal. Furthermore increased retention of fluid is common, at least temporarily. Only occasionally is this followed by a sufficiently large diuresis to account both for the administered sodium as well as for excessive sodium and water previously present in the extracellular fluid.

Correction of Abnormal Blood Electrolyte Patterns

In the course of the repeated administration of mercurial diuretics, several responses may be observed. Quite commonly sodium chloride and water are excreted in large and proportionate quantities; edema fluid disappears and there is no significant disturbance in the blood electrolyte pattern. A second type of response is that in which sodium and chloride are excreted in proportionately greater amounts than water, or else sodium, chloride and water are excreted in proportional amounts, but the water is partially replaced by drinking while extremely low sodium intake prevents restoration of this ion to a similar degree. In such cases a sodium depletion syndrome may occur. This is characterized by anorexia, vomiting, apathy, or stupor, azotemia, shock, hyponatremia, hypo-

chloremia and acidosis, among others. Continued administration of mercurials may lead to death while the administration of hypertonic sodium chloride may occasionally produce a dramatic clinic improvement, correction of the electrolyte disturbance and responsiveness to therapy.

A third response to the frequent administration of mercurials is a disproportionate excretion of chloride relative to sodium with a consequent reduction in plasma chloride, while plasma sodium is relatively unchanged. This hypochloremia is associated with a rise in plasma bicarbonate (alkalosis) and a reduction in plasma potassium (hypokalemia). This response to mercurials may be of importance because of the deleterious effect of alkalosis on renal function including the excretion of sodium, and because the development of this type of hypochloremic alkalosis is associated with unresponsiveness to mercurial diuretics. On the other hand if this abnormal electrolyte pattern is corrected by the administration of ammonium chloride, the clinical picture may improve strikingly, and diuretic responsiveness to mercurial drugs may be restored.

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ACUTE GASTRIC DILATATION

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Acute gastric dilatation was originally described in 1871 by Hans Kundrat, at one time Professor of Pathology at the University of Vienna and a contemporary of Theodor Billroth. Kundrat described autopsy reports of persons who had died with uncontrollable vomiting which was clinically usually attributed to peritonitis. The postmortem examination showed the stomach to be enormously dilated and filling almost the entire abdominal cavity and hiding all view of the intestines. On lifting the stomach out of its position, the duodenum was also found to be distended up to the point where the superior mesenteric artery crosses ventrally the third portion of the duodenum. In accordance with these findings, acute gastric dilatation was explained as a mechanical ileus under the name duodeno-jejunal ileus. The alternative name of arterio mesenteric ileus is based on the assumption that the pressure of the superior mesenteric artery upon the underlying third portion of the duodenum is responsible for the duodenal obstruction and leading to gastroduodenal dilatation.

Even the newest editions of surgical textbooks still cling to this conception. They advise a treatment consisting of putting the patient with arterio mesenteric ileus in a knee-elbow or in a steep Trendelenburg position, to bring the small intestine out of the pelvis and to release the downward pull on the superior mesenteric artery.

Arterio mesenteric ileus was always considered a rare type of mechanical obstruction. It was seen not only after abdominal surgery, but also following traumas of the spine and limbs, particularly fractures of the femur. It was not until the author became familiar with the methods of gastric aspiration and decompression (Levin tube, Wangensteen suction) that the author realized that acute dilatation of the stomach was far from being a rare occurrence. When a patient after an abdominal operation, after chest surgery, after fractures and trauma of the spine including the reduction of a spinal fracture and even without being operated upon, starts complaining of heartburn, belching, and hiccough, a tentative diagnosis of acute gastric dilatation can be made. The assumption of acute gastric dilatation is strengthened if the patient brings up small amounts of brownish or greenish fluid. A Levin tube should be passed and will detect in most cases the presence of large amounts of the identical greenish and blackish fluid in the stomach. These are the "storm water of a peat laden stream" (Bailey) of acute gastric dilatation. They contain chemically bile and components of pancreatic secretion which must have regurgitated from the duodenum into the stomach. We can safely assume that almost the entire duodenal secretions which amount to 500-1000 cc in 24 hours regurgitate. They produce hypersecretion of the stomach and this explains the enormous quantities of fluid obtained through gastric aspiration. There is a complete lack of all clinical signs pointing to the presence of a mechanical intestinal obstruction.

Acute gastric dilatation is a painless condition and even the vomitus becomes almost effortless. The onset usually escapes clinical attention until the patient complains of the above mentioned symptoms. It may take several days until the clinical picture becomes obvious and complete. In rare cases the onset of acute gastric dilatation is sudden and then usually accompanied by signs of shock.

The presence of bile in the stomach undoubtedly speaks for duodenal reflux into a stomach which has lost its tone. In the absence of mechanical obstruction, reflux takes place only when the propulsive action of the duodenum on its content toward the jejunum has ceased and the pyloric sphincter remains open. The assumption of paralytic or adynamic ileus of the duodenum and stomach is a most appropriate clinical explanation for this mechanism.

Until 1938 the author did all conventional upper abdominal surgery (cholecystectomies, partial gastrectomies) under anterior splanchnic anesthesia, blocking the celiac ganglia from the laparotomy wound. The pain interruption was perfect but the progress of the operation was frequently hampered by retching and vomiting. Therefore, to the injection of the celiac ganglia was added a novocain block of the vagus nerves around the cardia. Thereafter, no more retching and vomiting took place during the operations. All cases of partial gastrectomy operated upon in this way hardly ever required gastric aspiration. Furthermore, not a single case of acute gastric dilatation following an operation on the gall bladder or bile ducts was seen. On the other hand, when cyclopropane anesthesia was used, the situation changed completely. Gastric dilatation after cholecystectomy became a frequent complication.

A reflex origin of acute dilatation of the stomach under anesthesia, therefore, had to be assumed. This is not an entirely new conception. Dragstedt in 1931 drew the following picture of the mechanism of acute gastric dilatation. Afferent impulses from visceral or sensory somatic nerves which are stimulated during the operation reach the vagus center setting up first stimulation and eventual inhibition of the vagus nerves, thereby producing a clinical syndrome of acute gastric dilatation. This conception explains particularly well gastric dilatation following a gall bladder operation. Gall bladder and bile ducts receive an ample bilateral supply of afferent fibers which travel with the splanchnic nerves. The efferent impulses travel through the vagi to the stomach. The effect on the stomach is similar to that obtained by vagotomy for duodenal or marginal ulcer. The stomach and duodenum lose their intrinsic tone and motility, become flaccid and distended while the pylorus remains patulous and open. The duodenal content, which is under increasing secretory pressure, flows back into the stomach. The reflex arch can be interrupted by novocain blocking of the celiac and/or mesenteric ganglia.

Acute gastric dilatation can be explained only as being due to a reversible inhibitory visceromotor reflex. In the author's experience, it was particularly frequent after operations done under cyclopropane anesthesia. This anesthetic sensitizes structures innervated by the sympathetic and by this action probably promotes the appearance of the reflex syndrome.

A diagnosis of paralytic ileus should not be made until the possibility of acute gastric dilatation is excluded, by passage of a Levin tube and an x-ray flat plate of the stomach. A certain degree of adynamic ileus always accompanies gastric dilatation. It is successfully combated by gastric aspiration and by keeping the stomach and duodenum empty by continuous suction until their normal tone and motility have been restored. This leads, in turn and sometimes immediately, to reappearance of intestinal sounds and bowel evacuation (gastrocolic emptying reflex).

SUMMARY

Acute gastric dilatation is not a mechanical but an adynamic gastroduodenal ileus.

Acute gastric dilatation results from an inhibitory visceromotor reflex produced by trauma or painful stimuli during operation.

The afferent pathway of the reflex which inhibits gastric and duodenal motility runs with the sympathetic fibers.

Novocain blocking of the celiac ganglion interrupts the reflex.

Sympathomimetic anesthetics, e.g. cyclopropane, seem to sensitize the body for the reflex syndrome.

Developed acute gastric dilatation is a reversible condition. Preliminary or post-operative passage of a Levin tube will keep stomach and duodenum empty and enable them to regain their tone and motility which were lost by the activation of the reflex. Replacement of fluid and electrolyte loss will counteract the secondary damage resulting from dehydration and disturbed acid-base equilibrium.

The concomitant paralytic ileus does not require separate attention. It subsides with the disappearance of acute gastroduodenal dilatation.

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SOME OBSERVATIONS ON THE NUCLEIC ACIDS*

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The nucleic acids were discovered by Miescher just eighty years ago (1). It is particularly appropriate to discuss the nucleic acids at this time, the occasion of the eightieth anniversary of Professor Ernst Pick, who has been both the participant in and the witness to so many scholarly achievements.

Our knowledge of the nucleic acids did not evolve gradually, but rather in bursts of investigational enthusiasm such as that which prevails today. It is only in the last decade that the most exalted offices in the biochemical hierarchy have been attributed to the nucleic acids in both scientific fact and fiction. This acceptance and appreciation of the biological eminence of the nucleic acids is all the more remarkable, since even today we are uncertain of their chemical constitution, of their biosynthetic pathways, or of their chemical reactivities. Many roles are assigned to the nucleic acids on the sparsest circumstantial evidence, often simply because they have been observed at or near the scene of the action. And yet critical examination of many biological events not only reaffirms the primacy of the nucleic acids but often discloses new vistas.

A wholly new concept of the constitution of nucleic acid is emerging as a result of the multiplicity of biological discoveries alone. Until a few years ago there were two and only two nucleic acids; each was a tetranucleotide containing one equivalent of each of the four bases, the classical structures so conclusively epitomized by Levene. Now it appears that these formulae were but the products of intuition, conjecture, and an exaggerated sense of symmetry. Biochemists, under pressure by cytologists, began to re-evaluate and reorient the constituents of the nucleic acids; the classical formulae permitting only 12 permutations of each of the tetranucleotides had become inadequate for the rational comprehension of biological specificity.

Sufficient variation to permit a practically infinite series of specificities had to be found, and yet this sought-for variability was constrained to the narrow qualitative compositional parameters defined by no more than five or six nitrogenous bases and two carbohydrates. Since, in some instances at least, the functional capacities of the nucleic acids were closely related to their source, it also appeared reasonable that nucleic acid constitution should reflect species and organ differences.

Accordingly, new and ingenious, but often unconvincing, analytical techniques were devised, and applied to the analysis of a host of vague preparations euphemistically called nucleic acids. Criteria of purity were forgotten, and such a spate of numbers was produced as to disillusion all but the most devout on the very existence of the nucleic acids. The nucleic acid chemists now found them-

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selves in an awkward situation; forced to find new varieties of nucleic acid, they found them, but they could not rationalize their findings. They still sought a common formula which they had already denied in advance. Such are the semantic fallacies of our times!

But within these dissidences there lies, nevertheless, the basis of a rational explanation. Nucleic acids are commonly isolated from cells, tissues or organs, all substrates of great anisotropy. They are never to be found in homogeneously dispersed protoplasmic solution, but only in discrete particles in which all cells abound. In each of these particles resides some characteristic functional enzymatic system or systems; these particles in their harmonious proximity endowing the biological unit with its array of biochemical potentials. The mitochondria, for example, have been found to contain most, if not all, of the enzymes of the respiratory cycle; the chromosomes are presumed to carry all of the heritable determinants of the cell. To each particle, or even to each component enzyme of the particle, belongs its own determinate nucleic acid, whether as prosthetic group or as carrier, the combination particularizing the enzyme system.

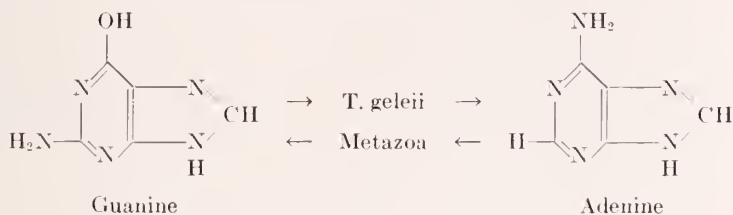
Thus there is ample teleological expectation of a large number of different nucleic acids, but by the same token there appears but meager probability that they can be identified by analytical techniques. Mixed nucleic acids only can be isolated, unless providentially it becomes possible to work with completely unifunctional, isotropic biological elements. The latter probability appears vanishingly small at this writing; even the chromosomes contain more than one nucleic acid. Indeed, there is good reason to believe that gene specificity may well involve nucleic acid dissimilarities. Virtually all the analytical data now swelling the journals is within reason and comprehension, but only in the sense that these data describe mixtures of nucleic acids.

Acceptance of this hypothesis carries a further implication in that it suggests the futility of searching for the mechanisms of drug action by estimation of the changes in nucleic acid concentration following the administration of the drug. One particular nucleic acid, one specific enzyme particle, might well be altered by the drug, but that alteration could well be lost sight of in the general cellular milieu. On the other hand gross mensurable changes in the cellular nucleic acids would be suspect since they could only result from massive nonspecific effects. It has been shown, for example, that liver ribose nucleic acid is diminished in starvation. It is probable, then, that any drug with toxic effects even secondarily affecting food intake, assimilation, or metabolism might reasonably be expected to bring about a reduction of total liver ribonucleic acid.

But this static analytical methodology is not the sole avenue of nucleic research. Dynamic studies, best exemplified in the employment of isotopic markers, illustrate again the complexities of nucleic acid in nature. It would appear that the terminology employed in cytology does not even approximately describe chemical events. Morphologic differentiation bears a specious suggestion of parallelism with enzymatic potentiality; it could be inferred that primitive, relatively undifferentiated protozoa might synthesize nucleic acids from any

source of nitrogen and carbon, whereas more highly differentiated metazoan cells should have an absolute requirement for preformed heterocyclic rings. But the facts are quite to the contrary; the literature is replete with examples. The metazoa convert amino acids and even complex compounds to nucleic acids, whereas some bacteria and protozoa, on the other hand, are known to reproduce only if one or more preformed purines or pyrimidines are added to the diet.

Even though animals do not require pyrimidines or purines they can and do utilize one and only one of them, namely, adenine, if it is offered to them, whether in the diet or parenterally (3). But, the utilization of adenine is always attended with a partial conversion to guanine. Thus if radioactive adenine is administered to an animal, the radioactive label is subsequently found in both the adenine and guanine moieties of the cellular polynucleotides. Rats and mice cannot utilize guanine at all. The protozoan, *Tetrahymena geleii*, on the other hand, depends on the presence of guanine in its growth medium (4). It has been shown that some of this guanine is in fact incorporated directly into the polynucleotides of the organism, but that an equivalent portion of the guanine is also converted to adenine, so that if isotopically labelled guanine is added to the diet, the label is subsequently found in both the adenine and guanine moieties of the organism (5). But this partial conversion of guanine to adenine occurs only in the absence of preformed adenine for in the presence of adenine the isotopic label of guanine is found in the guanine moiety alone (6).



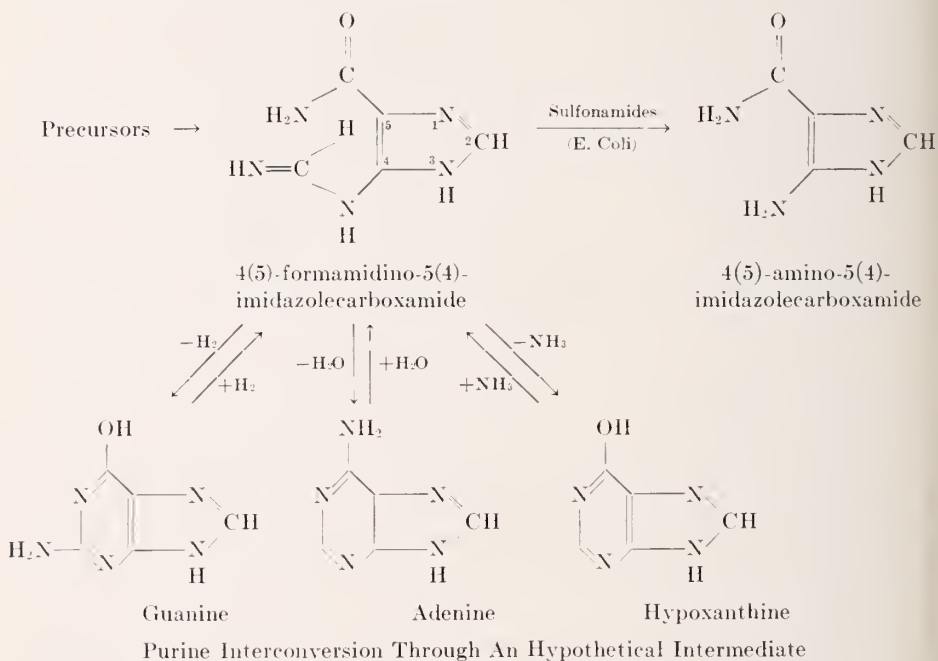
Comparison of Purine Incorporation by Metazoa and Protozoa

In the metazoa, then, the synthesis goes in one direction, adenine to guanine; in the protozoan it is reversed, guanine to adenine. In neither case is this process reversible. These facts raise the question of mechanism, a mechanism involving a common intermediate, susceptible to one set of reactions in the metazoa, and another set in the protozoa.

Actually this question of mechanism and a suggestive solution of the problem had anticipated and preceded the experiments on *Tetrahymena geleii*. Evidence had already appeared to suggest that an imidazole must be an intermediate in the biological synthesis of purines from compounds of a lower order of complexity. When sulfonamides were added to cultures of *E. coli* it was found that 4-amino-5-imidazolecarboxamide accumulated in the medium (7, 8). Now, this substance requires the addition of only one carbon atom and ring closure to produce a purine. The compound can, in fact, be utilized for purine synthesis in some systems, but it is not regarded as a normal constituent of tissues. It is not unreasonable to assume, on the other hand, that 4-amino-5-imidazole-

carboxamide was formed from purines in the sulfonamide treated *E. coli* by elimination of one carbon atom, indicating that a purine ring opening at or about carbon 2 does occur in nature. On this basis it is possible to write the structure of the hypothetical intermediate between adenine and guanine (9).

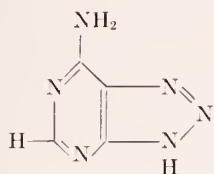
Hydrolysis of guanine between the 1 and 2 positions should yield 4-ureido-5-imidazolecarboxamide. Reductive ring opening, another biologically plausible reaction, would yield 4-formamidino-5-imidazolecarboxamide. On the other hand hydrolytic splitting of adenine between positions 1 and 2 would yield 4-formamido-5-imidazolecarboxamidine and if it took place between 1 and 6 would result in 4-formamidino-5-imidazolecarboxamide. This latter compound is obtainable also from guanine by a reductive type of ring opening. Conversely, closure of the ring by dehydration should yield adenine and by dehydrogenation should result in guanine. Conceivably, 4-formamidino-5-imidazolecarboxamide could yield hypoxanthine by loss of NH_3 . It is to be noted that all of these conversion reactions are biologically possible.



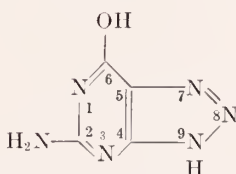
The conversion of guanine-8- C^{14} to adenine-8- C^{14} by *T. geleii* shows that all of the adenine arises from guanine without loss of radioactive carbon, indicating that ring opening does not involve the imidazole portion of the purine (5). Whether or not the pyrimidine ring also remains intact in the guanine-adenine interconversion is an unsettled experimental question (10). A common intermediate of the imidazole type in the biological synthesis of the purines is plausible. Further tracer studies and the testing of imidazole derivatives in appropriate systems may eventually clarify this point.

The protozoan *T. geleii* has occupied a prominent position in these studies. This is not wholly the result of its experimentally attractive requirement for guanine, but also arises from the curious procession of events following Kidder's discovery that 8-azaguanine could inhibit the growth of *T. geleii* (11). This inhibition, reversed by guanine or guanylic acid categorizes 8-azaguanine as a competitive inhibitor by virtue of its analogy to guanine. But Kidder then made an amazing guess, and administered the compound to tumor bearing animals with the result that tumor growth also was inhibited (12). This carcinostatic activity of azaguanine has been widely confirmed (13); it is effective against a number of experimental adenocarcinomas at high therapeutic index.

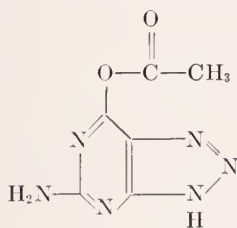
Seemingly, then, cancer tissues which are susceptible to the drug must be



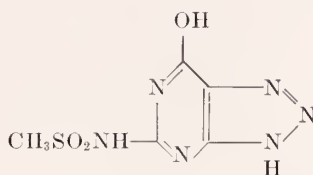
8-Azaadenine (Adenazolo)



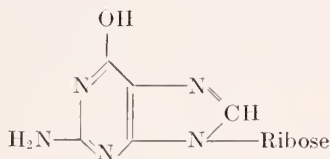
8-Azaguanine (Guanazolo)



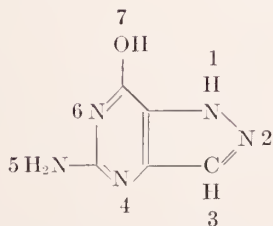
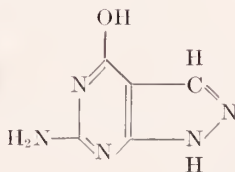
Acetylguanazolo



Sulfoxylate Derivative



Guanosine

5-Amino-7-hydroxypyrazolo
[4, 3-d] pyrimidine*5-Amino-7-hydroxypyrazolo
[3, 4-d] pyrimidine

Guanine Analogs in The Synthetic Study of Carcinogenic Activity

distinguished from normal tissues by a singular requirement for guanine. But this facile conclusion runs counter to the facts; it has been shown conclusively that guanine is not utilized at all by either normal tissues or azaguanine susceptible tumors (14). How, then, does the drug affect an unique cancer characteristic particulate enzyme system to bring about carcinostasis?

This question is under heavy experimental consideration with the real answer not yet in sight. Nevertheless, the structural similarity of guanine and 8-azaguanine has motivated the synthesis and testing of a number of other heterocyclic derivatives (15). But the specificity of 8-azaguanine is quite unique; even minor alterations, such as blocking either the amino or the hydroxyl function by simple acetyl or sulfoxalate groups are sufficient to abolish activity.

A curious dilemma is posed by the inactivity of 8-azaadenine, since the natural analog, adenine is itself readily incorporated into the polynucleotides of both normal and tumor tissue. Thus, the analog of the one nitrogenous base which is utilized is inactive, yet the analog of a compound which is not at all assimilated exhibits pharmacological activity which appears to be competitive in nature!

Among a number of other inactive compounds are the two pyrazolo-pyrimidines formed by substitution of a carbon for the nitrogen atoms at either the 7 or the 9 position of the guanine nucleus. These compounds are especially disappointing since it was anticipated that they might selectively inhibit the carbohydrate linkage which must occur early in the biosynthesis of the nucleic acids.

Not only has the search by synthesis so far failed to provide a clue to the mechanism of action of 8-azaguanine, but it has also failed to penetrate the wall of obscurity surrounding the biochemical reactivity of the many particle-bound nucleic acids. The former might well be a consequence of a flaw in the original premise; perhaps the structural resemblance of the compound to guanine is wholly adventitious, its carcinostatic activity only remotely, if at all, involving nucleic acid. In regard to the latter it could be opined that eighty years is perhaps too short a span to bring a science to maturity. The prospect of the future is bright and exciting with the promise that the chemists will catch up with the cytologists.

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THE USE OF DIBENAMINE IN PHEOCHROMOCYTOMA AND DETECTION OF PRESSOR ACTIVITY OF THE PLASMA BY BIO-ASSAY*

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In recent years use of a number of pharmacologic tests has enhanced our ability to diagnose pheochromocytoma with increased frequency.

If the pheochromocytoma is associated with paroxysmal hypertension, such paroxysms during the normotensive phase can be induced by histamine (1), mechohyl (2) or tetraethylammonium chloride (Etamon) (3). The mechanism for the induced paroxysm is ascribed to the ability of these agents to promote secretion of pressor substances contained in the tumor.

If the pheochromocytoma is associated with sustained hypertension, lowering of the blood pressure can be induced by benzodioxane (Benodaine) (4), Regitine (5) or Dibenamine (6, 7). The mechanism of the blood pressure reduction is ascribed to the adrenergic blockade induced by these agents.

These various pharmacologic tests are used as diagnostic aids to differentiate the adrenal medullary syndrome due to pheochromocytoma from simple paroxysmal or essential hypertension.

Since some of the above agents may influence the blood pressure in both of these conditions, only those agents exhibiting specificity of action in pheochromocytoma can be considered of diagnostic value.

A case of pheochromocytoma offered the opportunity to evaluate a number of these pharmacologic tests, including blood pressure responses to histamine, Etamon, Benodaine and Dibenamine. Hypertension associated with pheochromocytoma being due to circulating pressor substances, demonstration of the latter in the blood appears to be a most desirable approach. In our case such determinations were performed before and after the removal of the tumor using the Laewen-Trendelenburg preparation as a test object. In addition an extensive investigation of various functions of this patient was also carried out, the detailed results of which will be published elsewhere (8).

This paper deals chiefly with the results observed with Dibenamine[†] and those of the bio-assay for the detection of pressor substances.

CASE REPORT

Z. Z., (case # 49159) a 57 year-old white male was admitted to Montefiore Hospital on October 21, 1949 with chief complaints of vertigo, spells of blindness, sweating and a history of high blood pressure of several years duration. Between the onset of his symptoms in 1938 and his admission to Montefiore Hospital, his multiple and varied clinical manifestations led to the following diagnoses: toxic goiter, myocardial infarction, psychoneurosis, diabetes and arterial hypertension. After admission to this hospital it was found that he had sus-

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† Dibenamine was kindly supplied by the Smith, Kline and French Laboratories.

tained hypertension (240/140) and while hospitalized the patient had several spontaneous attacks of paroxysmal hypertension characterized by headache, palpitation, generalized profuse sweating and severe right flank pain radiating into the precordium. During these spontaneous attacks the systolic pressure was over 300 mm. Hg and the diastolic pressure over 200 mm. Hg. He also had hypermetabolism, and hyperglycemia with glycosuria.

The following diagnostic tests were carried out: The sedation test with sodium amytal reduced the blood pressure from 210/120 to 150/100. Following the intravenous administration of 1 c.c. (100 mg.) of Etamon the patient had pain in the back and the right lumbar region, followed by vomiting and profuse sweating. The systolic blood pressure rose to over 300 mm. Hg while the diastolic was 150 mm. Hg. Intravenous injection of 0.025 mg. of histamine base caused a rise in blood pressure to levels above 300 mm. Hg for the

Z. Z. ♂ Age 57 10/26/49 Pheochromocytoma

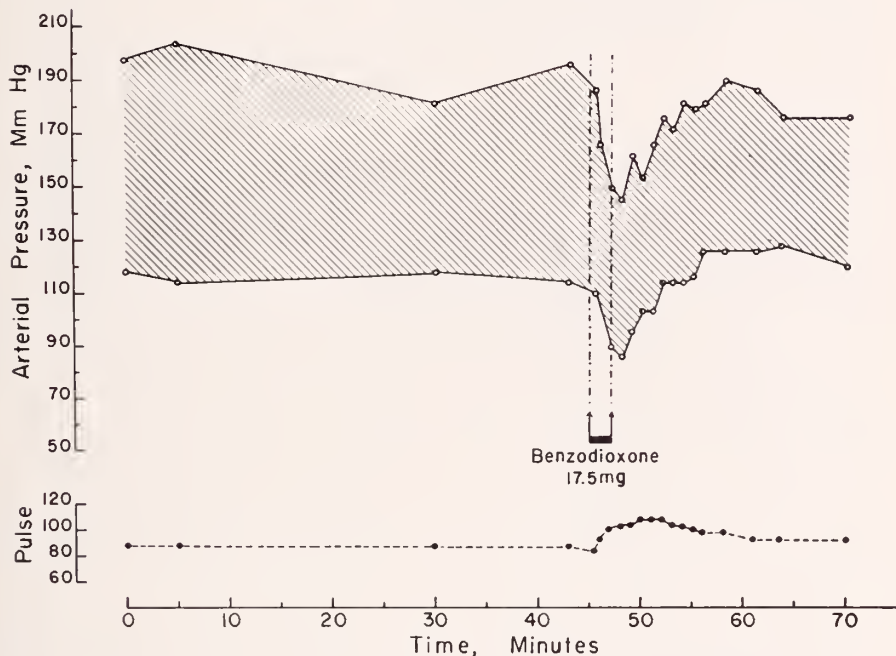


FIG. 1. Positive benzodioxane test in this case of pheochromocytoma

systolic and 200 mm. Hg for the diastolic. In addition to the blood pressure changes the patient had all the clinical manifestations which usually accompanied his spontaneous attacks. A benzodioxane test (fig. 1) performed on 10/26/49 showed a fall in blood pressure from 196/114 to 146/86 and a return to the initial level within 13 minutes. A first Dibenamine test, performed on 11/3/49, consisted of the intravenous administration of 5 mg. per Kg. body weight (total 300 mg.). One hour after its administration, the blood pressure fell from 224/120 to 172/90. A second Dibenamine infusion, given a week later in the dosage of 7.5 mg. per Kg. body weight (total 450 mg.), induced a marked and prolonged fall in blood pressure (fig. 2), from 212/120 to 105/70. It remained below control levels for 18 hours. During the time interval represented by the non-shaded area of Figure 2, an acute vascular response was induced by the intravenous injection of 0.025 mg. of histamine base. This response was omitted in this figure and is shown in detail in Figure 3. The effect of histamine base was induced during the height of Dibenamine blockade. While the arterial pressure was being recorded directly from the femoral artery with the electromanometer,

intravenous injection of 0.025 mg. of histamine was followed within 4 minutes by a rise in blood pressure from 100/50 to 250/100. This pressor effect disappeared within 10 minutes.

On both occasions, for 2-3 days following the administration of Dibenamine, the patient was less irritable, had no headaches or palpitation, and claimed to have a feeling of well-being not previously experienced.

After removal of the pheochromocytoma (operation performed by Dr. L. Orkin) the patient's blood pressure ranged from 150/80 to 200/110. All the above pharmacologic tests were repeated postoperatively. The tests performed with histamine, Benodaine and Etamon remained negative. But unlike these latter agents, Dibenamine still induced a fall in the resting blood pressure from 184/110 to 158/80. In addition, marked vasodilatation (90° - 92° F.) of the upper and lower extremities was noted within 1 hour after the completion of the infusion. Such peripheral vasodilatation was absent in the two preoperative tests with Dibenamine. Postoperatively, all the other metabolic tests reverted to normal values.

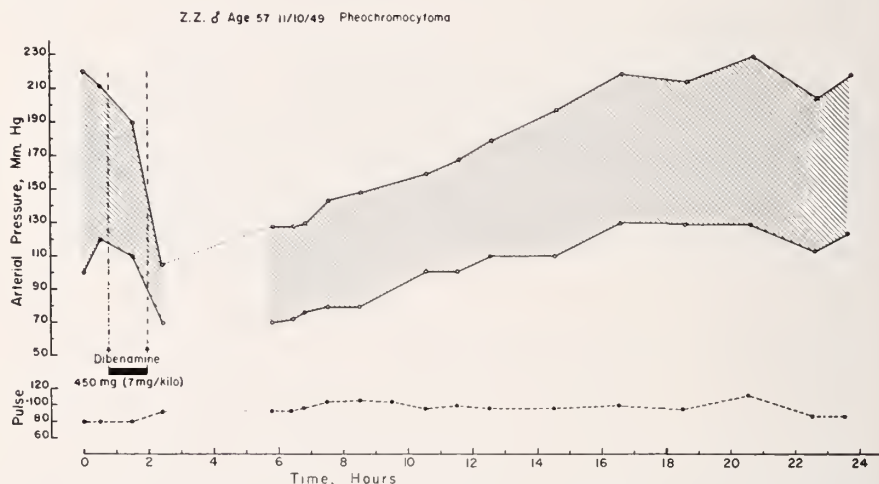


FIG. 2. Great and sustained fall in both systolic and diastolic blood pressures induced by Dibenamine in the same patient. The non-shaded area represents an acute vascular response to histamine omitted in this figure but shown in detail in Fig. 3.

Residual arterial hypertension after removal of a pheochromocytoma may be accounted for by either the presence of additional chromaffin cell tumor or essential hypertension. In the present case, the disappearance of paroxysmal attacks, the negative tests with Benodaine, histamine and Etamon, absence of circulating pressor substance, the disappearance of diabetes and improvement of the patient are all against the diagnosis of residual pheochromocytoma, and are in favor of that of essential hypertension.

Bio-assay test. Perfusion of the frog's hindlegs (the Laewen-Trendelenburg preparation) was used for the detection of circulating pressor substances by a method previously described (9). The blood was taken from an antecubital vein, all the steps of the blood withdrawal being handled under heparin (needle, syringe, test tubes). Two specimens of blood were taken, one before (Plasma 1) and one after administration of 0.025 mg. of histamine base to the patient (Plasma 2). The latter blood was taken during the maximum pressor effect of the histamine test. The blood was centrifuged immediately for 10 minutes at 1,500 R.P.M. The supernatant plasma was then transferred into another test tube, and the two specimens of plasma were tested immediately in the Laewen-

Trendelenburg preparation. Freshly prepared dilutions of epinephrine of different concentrations were also tested. The results of these tests are shown in

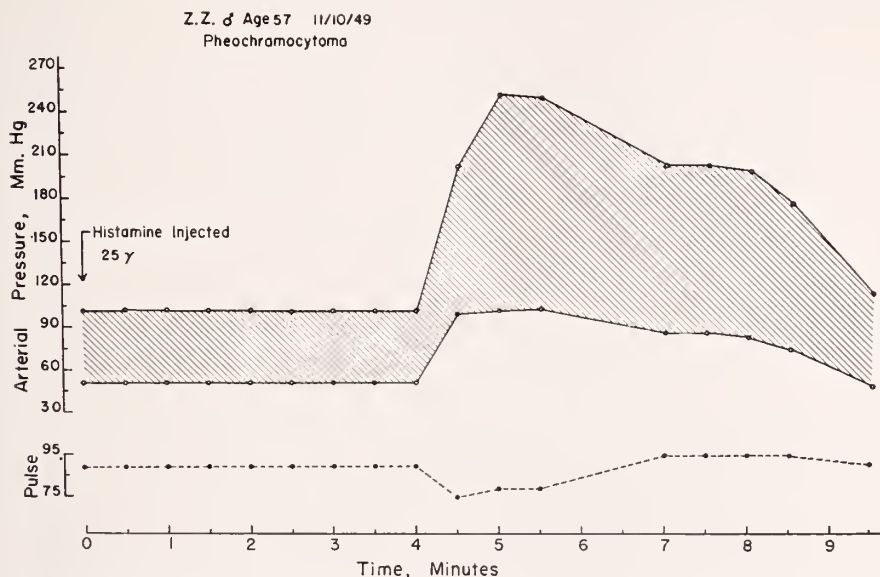


FIG. 3. Pressor effect of 0.025 mg. of histamine base during the height of Dibenamine blockade (see non-shaded area of Fig. 2).

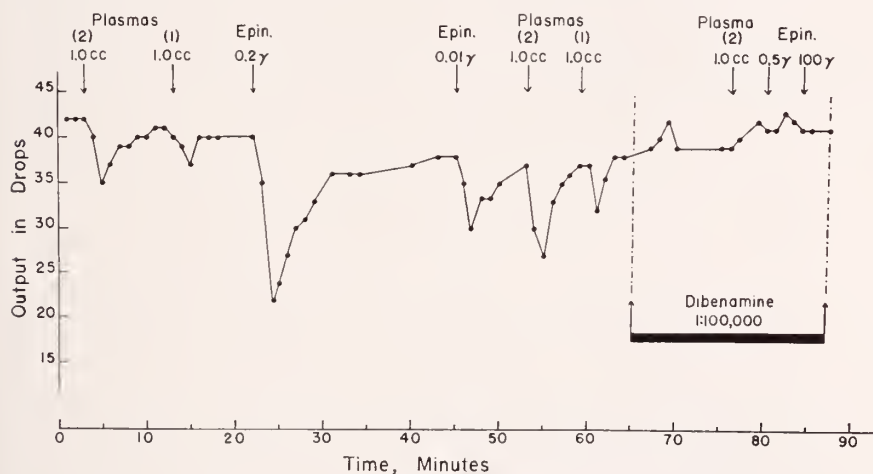


FIG. 4. Vasoconstrictor activity of heparinized plasma from this patient with pheochromocytoma tested in the Laewen-Trendelenburg preparation. Plasma 1 was taken before injection of 0.025 mg. of histamine, and Plasma 2 afterward. Vasoconstrictor activity of Plasma 2 as well as that of epinephrine was blocked after the preparation was perfused with Dibenamine.

Figure 4. It can be seen that both plasmas exhibited vasoconstrictor activity, Plasma 2 being more active than Plasma 1. The amount of vasopressor substance present in the post-histamine specimen exhibited grossly the equivalent activity of 0.01 gamma of epinephrine per c.c. of plasma. After the Laewen-

Trendelenburg preparation was perfused for 10 minutes with a 1:100,000 solution of Dibenamine, the pressor activity of the plasma as well as that of large amounts of epinephrine was completely blocked. The possibility that the vaso-pressor activity of the plasma could be ascribed to a vasoconstrictor substance derived from platelet disintegration can be ruled out since it is established that the use of heparinized plasma prevents the latter phenomenon (10). The relation of the plasma vasoactivity to essential hypertension can also be ruled out

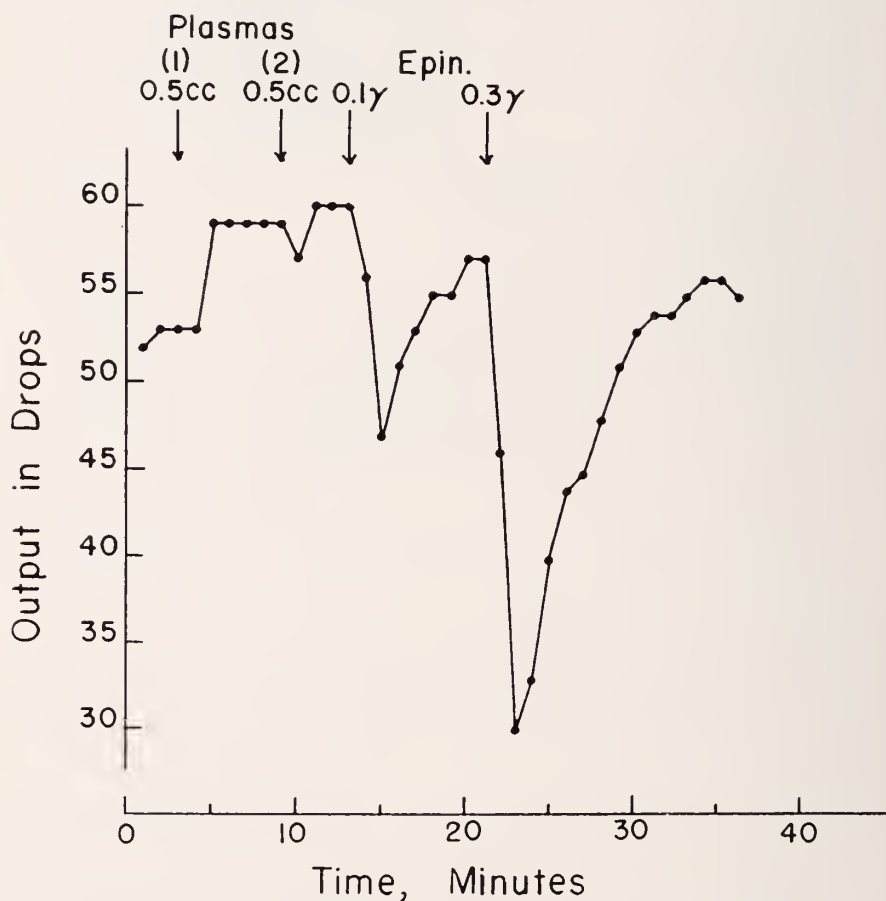


FIG. 5. Lack of vasoconstrictor activity of the same patient's plasma tested in the Laewen-Trendelenburg preparation after removal of the pheochromocytoma.

since heparinized plasma of such patients exhibits no vasoconstrictor action on the vascular bed of the Laewen-Trendelenburg preparation (11). The blockade by Dibenamine of the vasoconstrictor activity of the plasma therefore suggests that the latter contained either epinephrine or norepinephrine, or both since Dibenamine is a specific adrenergic blocking agent. One month after successful removal of the pheochromocytoma the above tests were repeated. Figure 5 shows that the plasma no longer exhibited any vasoconstrictor activity.

The diagnostic value of this bio-assay is difficult to assess. Demonstration of a

pressor substance in the blood preoperatively during hypertensive crises in a case of pheochromocytoma has previously been reported by Beer, King and Prinzmetal (12). These investigators used the isolated rabbit's ear as a test object. Shingleton and Baker (13) used a fluorometric method for determining adrenalin in the blood of a patient with pheochromocytoma. Others using a similar technique failed to demonstrate circulating pressor substances in the blood (14). Further experience with such techniques is necessary before establishing their practical value. However, it is of interest that in the present case the use of the Laewen-Trendelenburg bio-assay yielded results consistent with the diagnosis of circulating pressor substances and confirmed the other tests.

DISCUSSION

The clinical value of the pharmacologic tests in the diagnosis of pheochromocytoma is a well established fact. Histamine and benzodioxane seem to be the most useful agents because of their greater specificity in detecting the presence of pheochromocytoma. However, false positive and false negative tests have been reported with these agents (15, 16). Because of these failures, it is desirable that tests with other adrenergic blocking agents be performed, since it appears that a single pharmacologic test cannot be relied upon alone.

Among newer agents, Dibenamine has been used in the diagnosis of pheochromocytoma and was thought by some investigators to be specific (6, 7, 17, 18). However, Dibenamine exhibits not only marked "adrenolytic" but also "sympatholytic" properties. As previously reported (19, 20), Dibenamine is capable of inducing a fall in resting arterial blood pressure to normal or below normal levels in benign or moderately advanced essential hypertension, and also occasionally in malignant hypertension. It also induces orthostatic hypotension in both normotensive and hypertensive subjects. These findings were further confirmed by other investigators (21, 22). Since Dibenamine is capable of lowering the resting blood pressure of patients with both essential hypertension and hypertension associated with pheochromocytoma, this agent therefore cannot be considered as a specific diagnostic aid in the latter condition.

However, Dibenamine may assume some value if used in association with histamine, as reported by Spear and Griswold (17), Spühler, et al. (18), and as used in the present case. It should be pointed out that the specificity of the vascular responses following the use of these two agents in pheochromocytoma lies with histamine rather than with Dibenamine. In the two cases reported by these two groups of investigators, the patients had paroxysmal hypertension and administration of Dibenamine blocked the pressor effect of histamine. In the present case with sustained hypertension and paroxysmal attacks, Dibenamine like benzodioxane lowered the blood pressure to normal levels, but the histamine effect was not blocked completely. The pressor action of histamine during the hypotensive effect of Dibenamine observed in our patient is an interesting phenomenon which may prove to be a great aid in the diagnosis. This phenomenon may be accounted for by either insufficient adrenergic blocking dose of Dibenamine or release of a pressor substance other than epinephrine, such as nor-epinephrine, which Dibenamine is unable to block completely. The latter hy-

pothesis appears to be borne out by the fact that norepinephrine, of which these tumors have an unusually high content, is not always completely blocked by Dibenamine (23, 24).

The use of adrenergic blocking agents before surgery and during the operative removal of the tumor appears valuable in the prevention of blood pressure fluctuations. The effectiveness, specificity and prolonged action of Dibenamine recommend this drug more particularly in the management of these patients in the period before operation. As mentioned above, beneficial effects have thus been reported. Dibenamine in conjunction with surgery has been used by a few investigators in order to prevent extreme fluctuations of blood pressure during manipulation of the tumor, and thereby reduce the operative risk (25). If shock develops during the operative stage, neosynephrine and norepinephrine are capable of counteracting the blockade induced by Dibenamine. Epinephrine administered after Dibenamine has no effect on the blood pressure and is therefore contraindicated. This is illustrated by a case whose blood pressure fell to unobtainable levels after removal of a pheochromocytoma and in whom, because of previous administration of Dibenamine, epinephrine had no effect and the patient died (26). Because of possible vascular collapse, shorter-acting adrenergic blocking agents such as Benodaine or Regitine may appear more desirable in the management of this stage.

However, Cahill and Monteith (27) recently reported the administration of Dibenamine to two patients in the immediate postoperative period, and the use of norepinephrine in both cases immediately after the operation with good results. If this is confirmed in additional cases, the use of Dibenamine would greatly improve their surgical management, and is worthy of further investigation.

SUMMARY

1. The use of Dibenamine in the diagnosis and management of pheochromocytoma is discussed. It is concluded that since Dibenamine is capable of lowering the resting blood pressure of patients with both essential hypertension and hypertension associated with pheochromocytoma, this drug cannot be considered as a specific diagnostic aid in the latter condition. However, its usefulness in conjunction with other pharmacologic tests or its use in the preoperative management of patients with pheochromocytoma is promising and worthy of further investigation.

2. Demonstration of circulating pressor substance by the use of the Laewen-Trendelenburg preparation as a test object is reported. The diagnostic value of such tests is discussed.

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THE ECCRINOLOGICAL CLASSIFICATION OF GASTRIC MUCUS¹

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Exocrine glandular structures and their secretory products may be classified as merocrine, holocrine, apocrine, eccrine, homocrine or heterocrine, according to certain characteristics of the secretions themselves. The proper classification of gastric mucus has never been established on the basis of the characteristics of this secretion, although Popoff (1) has designated it "merocrine" by reason of the appearance of the gastric glands in tissue section under limited circumstances. It is the purpose of the present paper, therefore, to examine this classification in the light of certain properties of gastric mucus as revealed by studies in this laboratory.

The origin of this system of classification can be traced to Ranvier, who introduced the first of these terms in 1886 in his lectures on the mechanism of secretion at the Collège de France (2). At that time, Ranvier defined a simple dichotomy, in the following terms: "*Il y a des glandes dont les cellules se comportent de même, leur évolution les amenant à la surface de l'épithélium glandulaire où elles tombent pour former le produit même de la sécrétion. J'appellerai ces glandes olocrines, et par opposition je désignerai sous le nom de glandes mérocrines le second group de glandes, celles dont le produit de sécrétion est élaboré dans les cellules, au sein du protoplasma qui les constitue, produit de sécrétion qui se dégage les cellules restant en place.*" The words *apocrine* and *eccrine* were not mentioned by Ranvier at all, but first appeared in the literature in 1922, in a paper by Schiefferdecker (3) which contains an excellent analysis of the diverse systems which had been proposed up to that time for the classification of the cutaneous glands. Going a step further than Ranvier, Schiefferdecker divided *merocrine* glands into two subdivisions: 1) Those which separate a secretion from the secretory cells without losing any portion of the cell itself—designated *eccrine glands* (*e-glands*); and 2) those which eject a part of the cell along with the secretory product, the cellular residuum retaining the nucleus and continuing its essential function by the repeated regeneration of the secretion proper—designated *apocrine glands* (*a-glands*).

These words derive from the greek root *κρίνειν* (to separate) and the corresponding prefixes *μέρος* (part or fraction), *ὅλος* (whole or entire), and *ἀπό* (off or away, and therefore detached). Of all the definitions encountered in modern textbooks of histology, the clearest and most satisfactory are those given by Maximow and Bloom (4). *Merocrine secretion* is that type "in which the glandular cell remains intact throughout a cyclic process of formation and discharge, and then formation again, followed by discharge, and so on, of secretory products" (e.g., the glands of salivary, pancreatic, and gastric acid secre-

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tion). *Holocrine secretion* is the variety in which "the products accumulate within the cell body; the cell finally dies and is discharged as the secretion of the gland, new cells having arisen in the meantime to repeat the same cycle" (e.g., the sebaceous glands). *Apocrine secretion* is the intermediate type, in which "the secretion accumulates within the free end of the cell; after a time, this portion of the cytoplasm is pinched off but the nucleus and most of the cytoplasm are undamaged, and after a recovery period, the cell passes through the same process again" (e.g., the mammary glands). Thus, Schiefferdecker's eccrine sub-group is identical with Ranvier's merocrine group, and the term, apocrine, is essentially a third main division, representing characteristics intermediate between those of the merocrine and holocrine types. The latter view is evidently the one taken by Maximow and Bloom, Bailey (5), and Schaffer (6, 7), and there appears to be no good reason for retaining the fourth term, eccrine, at all. For our present purpose, therefore, we also have adopted this simple trichotomy.

Another subdivision of the merocrine group has been proposed by Schaffer (6), based on the possible multiplicity of secretory functions of any one gland; a *homocrine* gland is one in which all the cells elaborate the same secretion, and a *heterocrine* gland one which yields a mixture of two or more distinct secretory products. According to this extension of the classification system, the gastric gland as a whole is heterocrine because it pours out a fluid which is a mixture of secretions from the parietal, peptic and columnar cells; but each of these cells, considered alone, is homocrine because of the individuality of its secretion. This is true for man, dog and other mammals. In fishes, reptiles, and birds, however, it is widely accepted that acid and pepsin are together elaborated by a single type of gastric gland cell (8). If this be so, such a cell must likewise be classified as heterocrine.

Let us now consider the evidence concerning the cell content and opacity of gastric mucus from mammals; then, in the light of this evidence and the above definitions, we may proceed to establish the proper classification of this secretion. It is generally recognized that viscous mucus may be either transparent, opalescent, or opaque, depending on the type of stimulus employed to collect it. Nontransparent specimens sometimes derive their opacity from flakes of insoluble mucin or, more often, from suspensions of desquamated epithelial cells, but the occurrence of transparent mucus implies that the secretion can also be cell-free under some circumstances. Microscopic examination of smears of such transparent material confirms this implication.

In the early stages of our work, cell-free mucus could be obtained only in very small quantities, and never with any regularity. Nevertheless, these observations suggested that gastric mucus secretion is usually holocrine but that occasionally it may be merocrine as well. However, an extensive statistical study (9, 10) of the frequency of occurrence of epithelial cells in acid-free specimens of canine pouch mucus obtained with various stimuli, threw a wholly different light on this problem of classification. Not only was the variation in this frequency very extensive, but the occurrence of mucous epithelium in the specimens—and therefore the extent of desquamation—increased with increasing intensity of mucus-stimulating action. For example, the frequency of occurrence of specimens of wholly acellular mucus was only about 5% with a muc-

gogue of high stimulating power (5% clove oil emulsion), but it was as great as 93% without any overt stimulus whatever (i.e., isotonic saline to minimize mechanical stimulation of the surface epithelium by the collecting catheter alone). The volumes of cell-free secretion collected without the use of a mucigogue were always very small relative to those of samples collected with the aid of a stimulus for the same interval of time.

Such desquamation seemed to be not an integral part of the secretory process but rather an independent though simultaneous reaction to the mucigogue. Evidence in support of this independence was derived from careful microscopic examination of clove oil-stimulated specimens; smears of such opaque material usually revealed areas of the microscope field which were entirely acellular, even though the specimen as a whole was filled with columnar cells. This interpretation of the exfoliation of the gastric mucus cells—that it is not an essential part of the cytological process of mucus secretion—was finally validated by the finding that alkaline opalescent viscid mucus which is entirely and invariably free of columnar and other cells can be obtained in relatively large quantities by the topical application of an acetylcholine solution (1 mg/ml) to the mucosa of a Heidenhain gastric pouch (11). Essentially the same results attended the use of the other parasympathomimetic agents, mecholyl chloride (0.5 mg/ml) and pilocarpine hydrochloride (1 mg/ml)—which establishes the generality of this observation.

It must be concluded that mucus secretion in the dog's stomach (and probably in man as well, although other mammalian species have not been investigated in this respect) is solely a *merocrine* process. Desquamation, when it occurs, results from a secondary and independent reaction to certain topical irritants. The process entails a loosening of the cement substance with consequent liberation of the cells in entire palisades as well as individual cells, and it is promptly followed by the initiation of reparative reactions of the tissue. In contrast to irritant substances, vagomimetic agents induce none of this exfoliation when applied topically, even though their mucigogue action is at least as good as that of eugenol and clove oil emulsions which are also desquamatory agents. Hence, the mucus from the surface cells of the stomach must be placed in the same category as the HCl secretion from the parietal cells, which also is clear and entirely free of cells and cellular debris. This conclusion from physiological evidence is in accord with Popoff's classification of these two cell-types made on the basis of tissue studies (1).

The proper classification of gastric mucus is a most important matter in the investigation of the physiology of this secretion, because, apart from its cytological implications, it betokens a comprehension of one of the primary steps in the protective activity exercised by the gastric mucous barrier. Since 1860 (12), it has been held that the stomach is protected against autodigestion, and hence against peptic ulceration, by the layer of viscous mucus which coats its inner surface. As a result of our studies concerned with the relation of mucus physiology to the induction of adenocarcinoma of the stomach, this simple theory has been expanded to a two-component concept of the mucous barrier

(13). According to this new view, any destructive agent impinging on the gastric mucosa encounters the layer of viscous mucus as a first line of defense. If this be inadequate to withstand the attack so that the traumatic agent penetrates through to the layer of mucous cells beneath, then the cement substance is loosened, the injured epithelium undergoes desquamation, and its replacement sets in shortly thereafter. In the dog, we have seen this process of destruction taking place progressively until the mucosa was denuded completely of its crypts, even as far down as the necks of the gland tubules, yet within 36 hours the foveolae were completely replaced and the ability to secrete mucus once more restored (14). This easy shedding of the surface epithelium and especially its ready replacement under ordinary conditions make it appear that the layer of tall columnar cells immediately beneath the sheet of mucus constitutes a second line of defense. Were the mucous glands holocrine, as we at first suspected from our early study of mucus smears, this hypothesis of a two-component mucous barrier would not have been tenable. The present unequivocal demonstration that the mucous cells are merocrine, and that their exfoliation is an independent though frequently parallel reaction to irritation, thus lends support to this new hypothesis.

SUMMARY

Various terms used in classifying the exocrine secretions are reexamined. A review of the pertinent physiological evidence accumulated in this laboratory is found to prove conclusively that mucus secretion in the stomach is merocrine, in conformity with the inference of Popoff based solely on morphological observations. The implications of this classification regarding the concept of a two-component protective mucous barrier in the stomach are presented.

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THE INFLUENCE OF TOXIC AGENTS ON THE FEMALE GENITAL ORGANS

A BRIEF REVIEW

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The effect of toxic agents on the female sex organs depends on: 1) the chemical characteristics of these agents, 2) the method of administration, 3) the total amount and the concentration of the toxic substance, 4) the intensity and rate of its absorption, and 5) the sensitivity of the affected sex organ to the particular agent.

It is well known that the ovaries belong to the most sensitive organs of the body. Changes in climate, season, nutrition, nervous and hormonal influences, and general infectious diseases can cause profound anatomic and functional changes in the ovaries. It is therefore no wonder that many chemicals, while acting chiefly on some other organ or organs, may also influence the reproductive activity of the ovaries. The most sensitive constituent of the ovaries are the maturing follicles. Resting primordial follicles are more resistant and the ovarian stroma is the least sensitive constituent of the ovary. Toxic agents may have a lethal effect on the follicles and cause infertility, amenorrhea and precocious involution of the sex organs. If the ovaries are only mildly affected, they may continue to produce fertilizable ova. The germ plasma of these ova, however, may be defective and may be the cause of abnormal embryonic development and early abortion. Lead, alcohol and morphine are examples of such substances which affect the germ plasma and interfere with the normal development of the fetus.

Experimental investigations have shown that malformations and even true neoplasms can be induced in animals by chemical products of living or dead tissues, implanted into the blastocoele of the embryo, or by injection of toxic agents, such as 5 per cent of Zinc chloride into the gonad. It was also shown that complete or incomplete sex inversion can be provoked by the injection of heterosexual hormones into the embryo or the pregnant animal. These and other observations suggest the possibility that similar developmental disorders and apparently "spontaneous" benign and malignant neoplasms may result from the effect of extrinsic noxious chemical agents. Thus, the traditional supposition that some dormant cells, which were not utilized for the organization of the body, are the source of neoplasm, may be antiquated and may have to be dropped or modified.

Several toxic agents such as phosphorus and several bacterial toxins provoke necrosis and hemorrhages into the placenta, thus causing fetal death and abortion.

Strong uterine contractions are induced by various orally or parenterally administered drugs such as ergot and pituitrin as well as by the local application of most chemical agents. Any irritant of a chemical nature, such as Tincture of

Iodine, when applied to the endometrium, causes violent peristaltic and anti-peristaltic contractions of the uterus. The antiperistalsis is often responsible for the passage of the irritant substance through the tubes into the peritoneum where it causes serious, and often irreparable damage. Abortions induced in this way are very frequently followed by permanent sterility.

The vagina is very little sensitive locally, but readily absorbs water-soluble drugs and poisons.

Toxic substances may be introduced into the body intentionally either by the patient herself or by someone else with suicide, murder, interruption of pregnancy, addiction to narcotics, or the intention to stimulate sexual desire or orgasm as a motive. More often, however, the intoxication is unintentional, and results from hazardous occupations in certain industries, from erroneous over-dosage of drugs, or from mistaking poisonous substances for harmless drugs or food.

The following groups of injurious substances deserve special attention: 1) industrial poisons which adversely affect the female genital organs, 2) abortifacients, 3) drugs taken by addicts.

INDUSTRIAL AND ACCIDENTAL INTOXICATIONS

The increasing employment of women in industry leads to more frequent exposure of women to related toxic hazards.

Lead. This metal is used in many industries, as in potteries, paint factories, plumbing, electric accumulator works, diamond cutting, japanning, and enameling. It is one of the most frequent and important industrial toxic agents. It may enter the body by inhalation, ingestion, or through defects in the skin. The acetate, carbonate, oxide, tetraoxide, and chromate are the principal salts of lead which are responsible for industrial intoxications. Accidental lead poisoning may result from drinking water out of lead pipes, from lead-containing tin and enamel ware, from tin cans soldered with lead and from lead-containing paints.

Apart from numerous serious lesions in different organs, which produce the most conspicuous symptoms of chronic lead poisoning—anemia, intestinal colic, palsy, encephalopathia, arthralgia, nephritis, hypertension, arteriosclerosis—lead affects also the sex organs. The menstrual flow becomes scant in some patients and profuse in others. Abortions and premature deliveries are frequent. The abortions as a rule are the result of the primary death of the fetus caused by the lead which has passed the placental barrier. Degenerative changes in the placenta and anoxia of the fetus provoked by tetanic uterine contractions, are additional causes of fetal death. If the affected mother has given birth to viable children, the latter are as a rule feeble, mentally retarded and frequently die in early childhood. Passage of lead into the milk of the nursing mother represents an additional danger to the infant.

Mercury has a wide range of usage in industry. It is employed in the manufacture of thermometers, in the coating of mirrors. Its effect on the female worker is to reduce or even to stop the menstrual flow; it induces an abortion in the pregnant woman.

Thallium. It is used in dyeing, in glass manufacture, and in the production of rat poisons. Its total effect is to cause amenorrhea and loss of sexual desire in women, loss of sexual potency and atrophy of the testicles in men. Loss of hair is a conspicuous symptom of thallium intoxication. All these phenomena are, however, reversible. Thallium poisoning is also observed when it is used for epilation of the scalp in ringworm diseases.

Benzol and Nitrobenzol. These chemicals are widely used in industry. They cause chronic intoxication, when the fumes of these volatile agents are inhaled over long periods of time. Among other more conspicuous symptoms are anemia, agranulocytosis, general weakness, dizziness, headaches, and hemorrhages into the skin or the mucous membranes. The latter may cause uterine bleedings and abortions.

Arsenic. This is contained in various vermin poisons, agricultural insecticides and paints. It causes ulcerations in the female genitals and may also induce abortions.

Tobacco. This is believed by some to have an adverse influence on the sexual functions of women working in tobacco factories. However, it is still undecided whether this claim is justified.

ABORTIFACIENTS

Among the innumerable agents used since ancient times to induce abortion, there are some that are totally ineffective and harmless, such as chalk and other quack remedies. However, most abortifacients are far from being innocuous. An abortive agent which would cause the uterus to expel the fetus without causing serious damage to the mother does not exist. Moreover, there is no chemical agent which could be called a reliable abortifacient. The effect of an abortifacient depends not only on the agent employed but also on the individual reaction of the pregnant woman. It may be ineffective in one woman, cause abortion in another, and induces merely transient uterine contractions in still another woman. The stage of pregnancy, the simultaneous action of psychic, mechanical and thermal stimuli and the presence of disease may be decisive for the effectiveness of an abortifacient.

The abortifacients provoke uterine contractions either by direct action on the uterus or its nerves or by reflex action through irritation of the intestine, as in the case when drastic purgatives are employed. It may also act primarily on the central nervous system and stimulate the pathways leading from the brain through the spinal cord to the uterus. Other abortifacients cause hemorrhages in the decidua and impair the nutrition and the oxygen supply of the fetus. Much more effective than the ingested or parenterally applied abortifacients are those which are introduced into the uterus itself and incite violent uterine contractions leading to separation of the ovum from the uterine wall. It is impossible to give a complete enumeration of all abortifacients, and only a few substances most frequently used for this purpose will be mentioned.

Acids. Oral intake of acids may produce abortion by reflex excitation of the uterus from the corroded mucosa of the intestinal tract, by the strain of vomit-

ing, and, in women who survive for a longer time, by the resulting parenchymatous and fatty degeneration of the uterus and by decidual hemorrhages. Organic acids, such as oxalic, acetic, salicylic and citric, have been more frequently used than inorganic acids. Oxalic acid, by virtue of its calcium-fixing power, is a strong protoplasmic poison with the most marked effect on the heart and the central nervous system. It also diminishes the coagulability of the blood and causes hemorrhages in various organs. Salicylic acid is far less harmful, but also not without danger. It lowers the prothrombin production in the liver and, in large dosage or when taken for a long time, produces hemorrhages in the uterine mucosa.

Alkalies are tissue solvents, and hence they are still more dangerous than acids. The latter coagulate tissue protein and thus limit the extent of their deleterious action. When taken orally, alkalies produce a most severe gastroenteritis and cardiovascular collapse. Soap has been very popular for a long time as an effective abortifacient among laity. It was also recommended by some gynecologists as a paste (*Interruptin*) for legal interruption of pregnancy. However, severe local toxic effects, such as necrosis of the uterine wall and peritonitis, as well as grave lesions in other organs, such as the lungs, and a considerable number of fatalities, brought this method into disrepute.

Metals and Salts. Various metals and salts are generally reputed to be effective abortifacients. Potassium permanganate is one of the most commonly employed for this purpose, acting in small doses as an emenagogue. Of the heavy metals, lead and mercury are chiefly used as abortive agents. Lead poisoning, acute as well as chronic, may cause abortion by provoking strong tetanic contractions of the uterus and hemorrhages in the endometrium. Metallic mercury is not dangerous but is not effective as an abortifacient. Its salts, however, are notorious, extremely dangerous poisons when taken orally as well as when employed as a uterine douche. Several iron compounds, when effective, cause marked gastrointestinal irritations, nephritis and cardiovascular collapse.

Halogens. Intrauterine injection of Tincture of Iodine has been frequently used for artificial abortion because it is easily available and is reputed as an antiseptic. The injections cause violent uterine contractions which usually lead to abortion. The expulsion of the ovum, however, is frequently followed by salpingitis, pelviperitonitis and permanent sterility.

Phosphor-arsenic Group. Phosphorus poisoning resulting from attempts of abortion or suicide were, in the past when phosphorus matches were in great use, daily occurrences. The degenerative changes and hemorrhages caused by phosphorus in many organs explain its effectiveness as abortifacient and its deadly effect. Arsenic trioxide and other arsenical compounds have been less commonly used as abortives. Occasionally, antimony tartrate has been employed for this purpose. Bismuth which is somewhat related to arsenic and antimony is not a common abortifacient, but its compounds which are widely used therapeutically as in syphilis have an effect on the female genitals. They may produce hemorrhagic ulcerative lesions in the cervix and a black discoloration of the vagina. The latter is due to deposits of Bismuth sulfide in the papillary stratum of the vaginal wall.

Blood Poisons. Substances which convert hemoglobin into methemoglobin, such as potassium chlorate and nitrobenzol, have also been used as abortifacients. Such an interruption of pregnancy usually leads to the termination of the mother's life.

Plant and Animal Poisons. This group comprises the majority of abortifacients. The mode of action of these agents is not always clear. Some of them have a peripheral action and irritate the uterine muscle or the nerve endings in the uterus. Some, such as caffeine, nicotine, pilocarpine, picrotoxine, strychnine and physostigmine, act primarily on the central nervous system. Certain poisons, such as aloe, gamboge ipomea, purga and colocynth, owe their supposed abortifacient efficiency mostly to their drastic action on the intestine and a reflex excitation of the uterus. The abortive effect of some plants which contain large amounts of volatile oils is partly due to the stimulation of the central nervous system, partly to a reflex action on the uterus from the inflamed intestinal mucosa, and partly to a hyperemia of the pelvic organs with subsequent uterine bleeding. To this group belong camphor, cedar oil, thuja occidentalis, apiol, tansy, artemisia absinthium, rosmarinus officinalis, garden rue, savine, pennyroyal, asarum europaeum, nutmeg, saffron, cinnamomum cassia and ceylonicum, turpentine and ledum palustre. Other plant abortifacients are taxus baccata, humulus lupulus, paeonia officinalis, polygonum hydropiperoides, cotton-root bark, colchicum autumnale, helleborus niger and gratiola officinalis.

Oral intake and enemas of tobacco infusions, popular abortifacients, when effective, sometimes lead to a fatal outcome for the gravida.

Cantharidin, which is obtained from the Spanish fly, cantharis vesicatoria and from several other beetles, has also been used to induce abortion. Severe gastroenteritis and nephritis, and acute inflammation of bladder and urethra, are frequent complications.

ADDICTION POISONS

Alcohol. It is generally known that acute as well as chronic alcohol intoxication suppresses ethical and social inhibitions and thus increases the exposure to venereal infections and deteriorates marital relations. The sexual desire is often increased in drunkenness, but may be depressed in chronic alcoholism. The menstrual bleeding is sometimes increased and the menstruation irregular. The large number of children of some alcoholic mothers is no evidence of true high fertility, but rather only the consequence of uncontrolled sexual activity. The degenerative changes which were clearly demonstrated in the testicles of chronic alcoholics indicate a deleterious effect of alcohol on the gonads. Analogous changes may take place in the ovaries of alcoholic women. The detrimental effect of parental alcoholism on the offspring is evident from various mental and physical defects of the children. Certain amount of alcohol passes into the milk of nursing women and may have an adverse influence on the development of the suckling.

Morphinism gradually suppresses sexual libido, causes irregularities of menstruation, and finally leads to amenorrhea and sterility. These changes are however reversible and a successful withdrawal can restore normal sexual functions. Pregnancy of chronic morphine addicts usually terminates in abortion.

Cocaine increases sexual desire and may be responsible for sexual perversities which may disappear after cure of the addiction.

Hashish is said to have a stimulating influence on the sexual libido.

Mescaline which is habitually used by some Indian tribes in the southern states of USA and in Mexico stimulates sexual activity in acute intoxication, but chronic addiction depresses the sexual desire.

COMMENT

It is a tragic consequence of progress in civilization that it adds new dangers and diseases to the plagues which nature has inflicted on mankind. It is a most gratifying duty of physicians in private practice or in governmental service to watch carefully the effects of changing living conditions and occupations on the health of the involved people and to prevent ills arising from these changes, or at least arrest the resulting diseases in their initial stages.

SUMMARY

The toxic agents which affect the female sex organs are reviewed, and the characteristics of the main groups of industrial toxic agents, abortifacients, and addiction poisons, are discussed.

THE EFFECT OF THIOUREA ON MITOSIS IN RAT LIVERS DAMAGED BY CARBON TETRACHLORIDE*

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In previous communications (1) we reported that thiourea given in repeated large doses to rats induces mitoses in the liver. In most experiments the mitoses showed normal configuration and all mitotic phases were present. In some, however, a striking accumulation of metaphases was observed, and there were also structural changes of the mitotic figures, consisting mainly in scattering of chromosomes (dispersed arrest). The number of mitotic figures with scattered chromosomes was sometimes exceedingly high. Since only occasional mitoses are normally present in the livers of young adult rats, the appearance of numerous mitoses following the administration of thiourea and their accumulation in the metaphase stage suggests that thiourea possesses the ability to induce mitoses in the liver as well as to arrest them in one particular phase.

The present study was undertaken to demonstrate the mitosis arresting effect of thiourea in the liver. For this purpose a mitotic reaction of the reparative type was induced in the rats' liver by carbon tetrachloride and the effect of a single large dose of thiourea on these mitoses was studied.

MATERIAL AND METHODS

Young albino rats of both sexes, weighing 65 to 155 g, were used. Fifteen rats which served as controls received on 3 consecutive days intraperitoneal injections of carbon tetrachloride diluted with liquid paraffine. The doses of carbon tetrachloride ranged from 0.025 to 0.05 cc per animal. Thirty-two rats were given intraperitoneally 0.4 to 0.5 g thiourea in an aqueous solution simultaneously with the third injection of carbon tetrachloride. The rats succumbed or were sacrificed 1 to 7 hours after the last injection. The livers were removed, fixed in Carnoy's or Zenker's fluid and embedded in paraffine. Sections 6 μ in thickness were stained with hematoxylin-eosin.

The percentage distribution of mitotic phases was tabulated by counting 100 mitoses with respect to phase in the livers of 12 rats receiving carbon tetrachloride and a single dose of thiourea, and in the livers of 5 rats treated with carbon tetrachloride alone.

RESULTS

All rats receiving only the 3 injections of carbon tetrachloride survived. Their livers showed the well known changes caused by this drug, namely: fatty degeneration of the liver cells in the central parts of the lobule, hydropic vacuolization in the midzonal areas and occasionally central necrosis. Mitoses were present in 11 out of 15 animals; in 5 rats they were numerous while in 6 only single mitoses were found. The presence and frequency of mitoses corresponded to a certain extent to the degree of hepatic damage. The mitotic figures were situated

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in the liver parenchyma adjacent to the damaged area. All phases of mitotic division were present and no structural changes were observed (fig. 1). The percentage distribution of mitotic phases in the livers of the 5 rats with numerous mitoses is tabulated in chart 1.

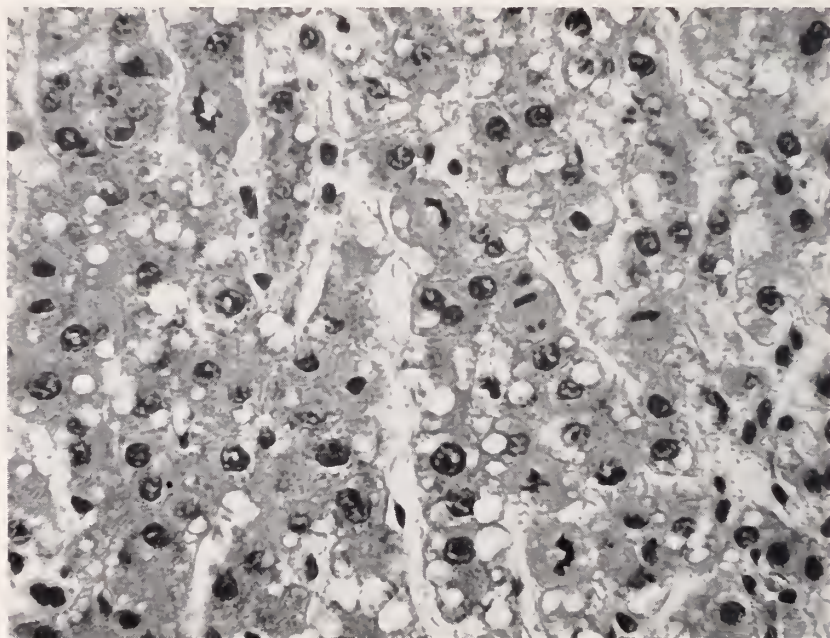


FIG. 1. Liver of rat No. 710 treated with carbon tetrachloride. Numerous mitoses in various phases.

CHART 1

Percentage distribution of mitotic phases in 100 mitoses counted in livers of rats treated with carbon tetrachloride

ANIMAL NUMBER	WEIGHT (G)	DOSES OF CARBON TETRACHLORIDE (CC)	DURATION OF EXPERIMENT (HOURS)	PROPHASES %	METAPHASES %	ANAPHASES %	TELO-RECON- STRUCTION PHASES %
R 739	95	3×0.04	53	12	64	10	14
R 738	110	3×0.04	53	8	63	20	9
R 710	140	3×0.05	52	4	55	33	8
R 585	70	3×0.025	53	18	63	12	7
R 574	150	3×0.025	53	9	48	20	23

The histological picture of the livers of rats receiving both carbon tetrachloride and thiourea was essentially the same as in those treated with carbon tetrachloride alone. The nature and extension of the hepatic damage in the livers of both groups was very similar. Twenty out of 32 rats treated with both drugs showed numerous or very numerous mitoses in the liver, 7 showed single mitoses, and in 5 no mitoses were present. The percentage distribution of mitotic phases in the livers of 12 of the animals which showed abundant mitoses, is given in chart 2. In all these experiments an accumulation of mitoses in the metaphase

stage was observed (fig. 2). The number of prophases as well as of the later phases (ana-telo- and reconstruction phases) was very low.

CHART 2

Percentage distribution of mitotic phases in 100 mitoses counted in livers of rats treated with carbon tetrachloride and thiourea

ANIMAL NUMBER	WEIGHT (G)	DOSES OF CARBON TETRA- CHLORIDE (CC)	DOSES OF THIOUREA (G)	DURATION OF EXPERI- MENT (HOURS)	TIME AFTER ADM. OF THIO- UREA HRS.	PRO- PHASES %	META- PHASES %	ANA- PHASES %	TELO- AND RECON- STRUC- TION PHASES %
570	65	3×0.025	1×0.4	52	4	0	96	4	0
595	75	3×0.025	1×0.4	51	3	0	96	3	1
596	75	3×0.025	1×0.4	52	4	2	94	2	2
597	70	3×0.025	1×0.4	49	1	0	91	8	1
713	120	3×0.04	1×0.5	52	4	1	87	5	7
689	110	3×0.03	1×0.4	50	2	0	82	13	5
690	105	3×0.03	1×0.4	51	2	0	87	11	2
676	155	3×0.05	1×0.4	53	5	8	78	10	4
580	65	3×0.025	1×0.4	50	2	0	98	2	0
730	120	3×0.05	1×0.5	53	5	1	80	13	6
735	130	3×0.05	1×0.5	53	5	4	82	11	3
734	130	3×0.05	1×0.5	53	5	3	87	9	1

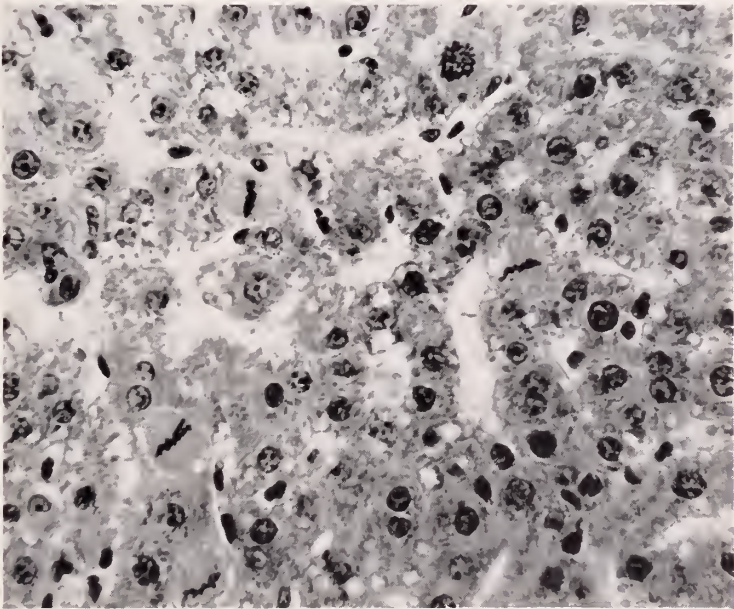


FIG. 2. Liver of rat No. 690 treated with carbon tetrachloride and thiourea. All mitotic figures are in the metaphase stage. They show no structural alterations.

The mitotic figures in the livers of rats receiving the combined treatment also showed structural alterations consisting of scattering of chromosomes. The chromosomes were not situated regularly in a metaphase plate but were dis-

persed throughout the cytoplasm (fig. 3). They were not rodlike as usual but formed ovoid or roundish granules. In some liver cells larger chromosome aggregates were dispersed throughout the cell body. These structural abnormalities were limited in some experiments to only a few metaphases, in some, however, most of the metaphases were involved.

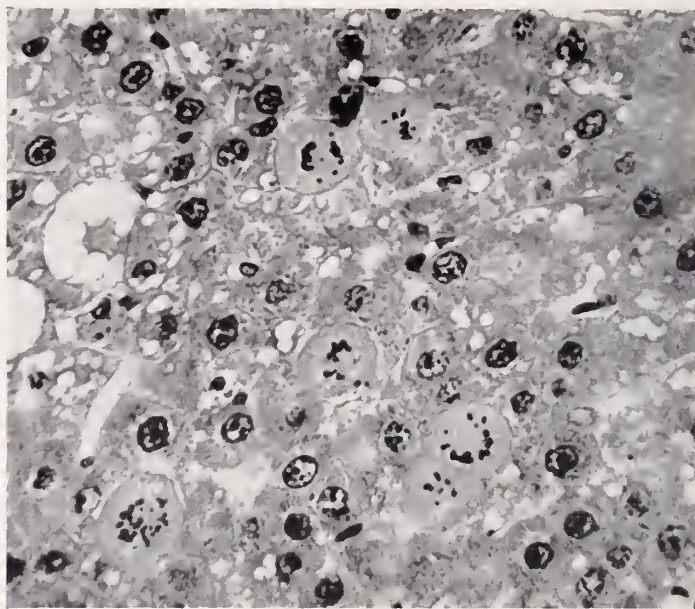


FIG. 3. Liver of rat No. 596 treated with carbon tetrachloride and thiourea. Accumulation of mitotic figures in the metaphase stage showing scattering of chromosomes.

DISCUSSION

According to our previous observations (1) mitoses appear in the livers of thiourea treated rats only after a latent period of 48 hours. In the present experiments, with combined carbon tetrachloride and thiourea treatment, the animals succumbed or were killed 1 to 7 hours after the administration of a single dose of thiourea, at a time when no induction of mitoses by thiourea could be expected. The mitoses present in the liver under these conditions were of the reparative type in response to liver damage caused by carbon tetrachloride.

In the livers of the control animals which received only carbon tetrachloride, mitotic figures in all phases and without structural alterations were found. The average percentage distribution of mitotic phases was: prophases: 10.2, metaphases: 58.6, anaphases: 19.0, telo- and reconstruction phases: 12.2. Similar proportions were found by Brues and Marble (2) in the regenerating liver of rats 24 to 49 hours after partial hepatectomy. Analysis of the data given in table V of their paper shows: prophases: 13.4, metaphases: 53.1, anaphases: 22.1, and telophases: 11.3.

The mitoses occurring in the livers of rats treated with both carbon tetra-

chloride and thiourea showed quite a different distribution of mitotic phases as well as marked structural changes. The average percentage distribution of mitotic phases in these livers was: prophases: 1.5, metaphases: 88.5, anaphases: 7.5, and telo- and reconstruction phases: 2.5. This distinct difference in the phase distribution can only be due to thiourea which when acting upon mitoses already present, arrests them in the metaphase stage.

This effect of thiourea in arresting mitosis was also observed by Rosin, Tenenbaum and Doljanski (3) on chicken heart fibroblasts cultivated *in vitro*.

The scattering of chromosomes as the characteristic structural alteration in mitotic figures caused by thiourea corresponds to the type designated as dispersed arrest by Paletta and Cowdry (4). It is due to suppression of spindle formation. This type of mitotic alteration was first described by Brues and Jackson (5) in livers of rats subjected to partial hepatectomy and subsequently treated with colchicine. Dustin (6) observed mitoses with scattered chromosomes in the liver of a human subject poisoned with colchicine. The same type of alteration was described by Miszurski and Doljanski (7) in livers of non hepatectomized rats after repeated injections of colchicine. Scattering of chromosomes was also observed by the present authors (1) in the livers of rats treated with repeated doses of thiourea. The experiments reported in this communication explain this phenomenon. The mitoses induced in the liver by thiourea can be arrested by the action of an additional dose of this drug, resulting in abnormal distribution of mitotic phases and dispersed arrest.

Like colchicine, which according to Miszurski and Doljanski (7) when given in repeated doses can induce and arrest mitosis in the liver, thiourea too has a twofold effect on this organ. It provokes mitoses in the liver cells and is also capable of arresting them.

SUMMARY

Young adult rats were given three successive intraperitoneal injections of carbon tetrachloride. After this treatment mitoses of the reparative type appeared in the liver. The mitoses were normal and all mitotic phases were present.

In another experimental series rats received a single intraperitoneal injection of thiourea simultaneously with the third injection of carbon tetrachloride. In the livers of these rats an accumulation of mitotic figures in the metaphase stage was observed. In some cases the arrested mitoses showed structural alterations consisting of scattering of chromosomes.

On the basis of these and previous experiments it is concluded that thiourea possesses the ability not only to induce but also to arrest mitosis in rat livers in one particular phase.

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LABORATORY AIDS IN THE DIAGNOSIS OF HYPERTHYROIDISM*

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More than a century and a quarter has elapsed since the clinical picture of hyperthyroidism was delineated by the clinical observations of Parry, Graves, von Basedow, Marie and others. As in many other fields in clinical medicine, it was not until the present century that the laboratory has been able to make its contribution to the understanding of this disease and it is only in the last decade that physical science has joined the other disciplines. It is therefore, not unfitting that both of us, who received their early scientific training as students and co-workers of Professor Pick, join in this tribute to him. It is particularly appropriate that thyroid disease and iodine metabolism be the subject of this report because Doctor Pick's (1) early papers on the alteration encountered in experimental hypothyroidism and his studies on artificially iodinated proteins are still classics in their field even if they are not remembered as often as their value justifies.

Basal Metabolism

As early as 1892 Friedrich Müller (2) had established the negative nitrogen balance that occurred in hyperthyroid patients with active disease and in 1895 Magnus-Levy (3) published his classical studies on oxygen consumption and carbon dioxide excretion in hyperthyroidism and in normals under the influence of thyroid extract. It is interesting to observe that one patient served to establish the calorogenic activity of thyroid extract and that three patients with hyperthyroidism were compared to three normals to establish the increased oxygen consumption in Graves' disease.

With the progressive simplification of the apparatus for the determination of oxygen consumption and its application to very large groups of patients by Du Bois and Boothby and Sandiford in this country this method came to be accepted as a very reliable indication of the functional state of the thyroid gland. There has been a recent tendency to minimize and even to abandon this simple procedure. We are not convinced that such an attitude is justified, aware as we are of its limitations. It was Magnus-Levy himself who first pointed out that there were occasionally encountered instances of increased oxygen consumption that were not dependent upon thyroid disease and one of us recently described the syndrome of "hypermetabolism without hyperthyroidism" as encountered in diverse conditions where thyroid function was shown to be normal by studies of the protein-bound iodine of the serum and the uptake of I-131 by the thyroid gland. Recognizing and accepting these limitations of the value of the basal metabolic rate, there is no doubt that it remains a very valuable laboratory method in the study of thyroid function and long experience has shown that a

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I-131 supplied on allocation by The United States Atomic Energy Commission.

consistently normal basal rate, while not pathognomonic of the euthyroid state, is very strong evidence against active hyperthyroidism. The simplicity and availability of this method and its proved usefulness will insure its survival among those who do not desire to be "the first by whom the new is tried nor yet the last to lay the old aside".

It must be remembered that the so-called "new" tests, particularly the blood iodine and studies with radioactive iodine do not measure the same thing as is measured by the basal metabolic rate. This alone will measure the total metabolic activity of the organism and this information, whether one chooses to interpret it or not, is not supplied by any of the other laboratory methods applied to thyroid disease. One must agree with Kendall (4) that "other factors being standard, the basal metabolic rate is a reliable index of the activity of the thyroid".

It is interesting to note that the determination of the basal metabolic rate, the level of the blood cholesterol and the serum protein-bound iodine all measure the effect of thyroid function in an area removed from the gland while the newer tests involving the use of radioactive iodine are a direct approach to the thyroid gland itself and an attempt to study the functional state of the gland during the immediate period under observation. From a historical point of view, therefore, earlier studies had to do with the effects of altered thyroid function as reflected in the areas of final physiological action of the hormone whereas the newer tests invade the gland itself and study its dynamics so far as they relate to formation and liberation of its specific secretion.

Blood Cholesterol

Epstein and Lande (5) in 1922 were the first to point out the relationship that existed between the functional state of the thyroid gland in human subjects and the level of the blood cholesterol. These studies were made in the Mount Sinai Hospital and their general validity has been confirmed many times. There is no doubt that hypothyroidism is generally accompanied by serum cholesterol values above normal and low or normal values are usually found in hyperthyroidism. However, the value of this determination as a specific diagnostic test is severely limited because there are many other diseased states that tend to raise or lower the cholesterol level in the serum. It is well known that hypercholesteremia is frequently encountered in obstructive jaundice, nephrosis, the lipoidoses, diabetes, and as a familial anomaly. Contrariwise, the cholesterol levels may be depressed in extensive liver disease, extreme cachexia and other states. In view of these many non-thyrogenous causes of disturbed cholesterol metabolism it is obviously unwise to use the blood cholesterol level as the sole index of thyroid function. In our experience, the serum cholesterol has not been of very great use in the diagnosis of hyperthyroidism. High levels are usually associated with myxedema.

Protein-bound Iodine (P.B.I.)

The first significant determination of the blood iodine was made by Gley and Bourcet (6) in 1900. They required a litre of blood for a single determination but

the value they obtained was not very different from what we now accept as normal. It is interesting to note that in this study, now almost completely forgotten, Gley and Bourcet not only determined the concentration of the normally circulating blood iodine, but proved that it was bound to protein, contained exclusively in the plasma and that the red cells were practically iodine free. A great deal of needless controversy that raged in the 1920's and 1930's could have been avoided if proper attention had been paid to this work.

The first comprehensive studies of the relation of the blood iodine level to thyroid disease were published by Veil and Sturm (7) in 1935. They clearly demonstrated that the blood iodine was elevated in hyperthyroidism and returned to normal when the hyperthyroid state was corrected. A large number of reports have now established this fact beyond doubt and the determination remains as one of the best single indicators of thyroid function.

The methodological difficulties can be understood when it is realized that less than one-millionth of a gram of iodine is determined in 10 ml. of serum and before that can be done the proteins must be destroyed, the iodine recovered and isolated. Earlier methods based on Rabourdin's (8) original alkali fusion were in general use until Leipert (9) introduced a wet digestion with sulphuric and chromic acids. This method was modified by Matthews (10) in 1938 and it was only after his report that most laboratories were able to obtain consistent results. It is interesting to note that the original method employing alkali fusion has most recently been re-employed by Salter (11) and Barker (12) with excellent results.

The methods are still difficult and tedious and specially trained technicians are required but a well equipped laboratory can master the problems in a reasonable period of time. We have had a wide experience with many thousands of determinations and are greatly impressed with their value. With the methods in general use the normal range for the P.B.I. is 4-8 gamma per 100 ml. of plasma or serum. Hyperthyroids give values above 8 and hypothyroids give values below 4. High values are encountered only in hyperthyroidism and occasionally in pregnancy. False high values may be obtained if organic compounds of iodine such as are used in cholecystography or intravenous urography have been administered. Lipiodol, thyroid extract and other organically bound iodine compounds also give false high values because they are bound to the plasma proteins and cannot be separated from them by methods presently available. Valid determinations can be made in the presence of administered Lugol's solution or inorganic iodides because these do not form complexes with the serum proteins and can be quantitatively separated from the P.B.I. by dialysis or precipitation and washing of the proteins. There is some evidence that recent administration of mercury salts may give rise to false low values. We have not found this to be so with the mercurial compounds now commonly used as diuretics.

Radioactive Iodine Studies

In 1938 small amounts of radioactive iodine (I-130) became available for experimental use and they were rapidly applied to the diagnosis and treatment of thyroid disorders by Saul Hertz (13) and his co-workers. It was soon established,

in confirmation of the earlier studies by David Marine (14), that the hyperactive gland of Graves' disease concentrated and fixed larger amounts of inorganic iodine than did the normal gland and that diagnostic use could be made of this phenomenon. These studies were widely extended in 1946 when large amounts of the more suitable isotope, I-131, became available from the atomic pile at Oak Ridge. It is now possible to administer a very small, the so-called tracer, dose of radioactive iodine by mouth and by suitable measurements determine the fraction of this dose which is fixed in the thyroid gland in a definite time, usually 24 hours. Hyperactive glands fix a large proportion of the administered dose, inactive glands as encountered in myxedema or after the administration of thyroid extract concentrate only a small fraction and the normally functioning gland gives values between these two extremes. The technique of measurement is relatively simple and active cooperation by the patient is not required. The subjective difficulties that are encountered in the basal metabolic rate determination are eliminated. As determined by this method euthyroid patients fix from 20 to 40% of the ingested dose of I-131 in the thyroid gland in 24 hours. Hyperthyroid patients fix more than 40% and myxedematous subjects fix very small amounts, usually less than 10%. Because of certain technical difficulties with measurements over the thyroid gland some observers have found it advisable to determine the amount of I-131 excreted in the urine in the same 24 hour period following the tracer dose. This measurement is simple and accurate but is valid only if quantitative urine collections can be assured and if there is no impairment of renal function to interfere with the excretion of the I-131. It is obvious that urinary excretion will bear a reverse ratio to gland uptake. Urinary excretion of I-131 has been the method generally used by us and values of less than 20% excretion in 24 hours are generally found in hyperthyroidism. Values of 30% or more are the rule in normals and hypothyroid subjects excrete 70% or more. In the range between 20 and 30% there is a considerable overlap between the normals and the hyperthyroids. This overlap could not be correlated with the degree of clinical activity. Some patients that were unequivocal clinical examples of active hyperthyroidism gave excretion values that were not consistent with the clinical diagnosis. The same difficulty was encountered when the uptake of I-131 by the thyroid was studied.

In order to refine further the diagnostic use of radioactive iodine we (15) have recently developed a new test based on the determination of the radioactivity in the blood after tracer doses of I-131. This test depends on the fact that the hyperfunctioning gland should deliver to the circulation larger amounts of hormone than the normal gland. Hormone formed after the administration of I-131 is tagged with this substance and can be detected and measured in the circulating blood. The labelled hormone circulates in a form bound to protein so that the measurement of the protein-bound I-131 of the plasma should give some idea of the rate of delivery of newly formed hormone to the circulation. This proved to be true and we (16) have reported the results of a consecutive series of 310 observations evenly divided between euthyroid and hyperthyroid patients. In only three cases has this new test failed to establish the correct diagnosis and

in these three cases false low values were obtained in hyperthyroidism. Not a single euthyroid subject gave values in the hyperthyroid range. It has been found that a single blood specimen of a few cubic centimeters drawn 72 hours after an oral tracer dose of 100 microcuries of I-131 will supply all the diagnostic information required. If the count in the whole plasma is low no further manipulation is required and the diagnosis of hyperthyroidism can be excluded with a high degree of certainty. If the count in the whole plasma is high it is then necessary to precipitate and wash the plasma proteins and determine the activity due to protein-bound I-131 because only the protein-bound I-131 represents thyroid

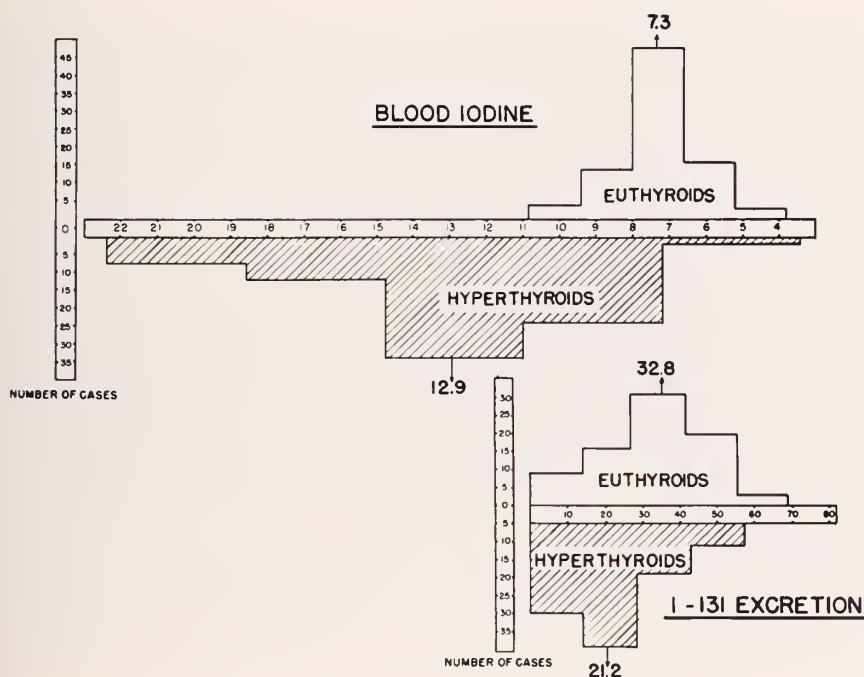


FIG. 1. The distribution of the cases of euthyroidism (85) and hyperthyroidism (79) plotted according to the blood iodine levels (P.B.I.) and the excretion of I-131. Each horizontal division represents one standard deviation on the corresponding scale.

activity. The inorganic I-131 which may contribute to the total plasma radioactivity is circulating only because it has not been excreted by the kidneys or trapped by the thyroid. Such situations have been encountered in renal disease or from "pre-renal" causes and bear no relation to thyroid function. In our experience this test has been the most valuable of all studies involving the use of I-131 in the diagnosis of thyroid activity. The value of this test, as all other tests using I-131 in diagnosis, is destroyed if iodine in any form, anti-thyroid drugs or thyroid extract have been administered shortly before the study is made.

At this point it might be helpful to present some of the data that we have collected. Figure 1 is a representation of the protein-bound iodine values and the I-131 excretion values obtained in a series of 85 euthyroid and 79 hyperthyroid

patients where there was no doubt as to the final diagnosis. It will be seen that the protein-bound iodine showed a better correlation with the final diagnosis than did the I-131 excretion.

In Figure 2 we present the data on 310 consecutive cases where the protein-bound I-131 of the plasma was determined. It will be noted that in every instance where the activity exceeded four counts per second per ml. of plasma (0.0003 microcuries I-131) the patients were hyperthyroid. In all but three instances euthyroid patients had counts below this level. This series has now been extended to more than 500 cases and we have yet to encounter a single example of

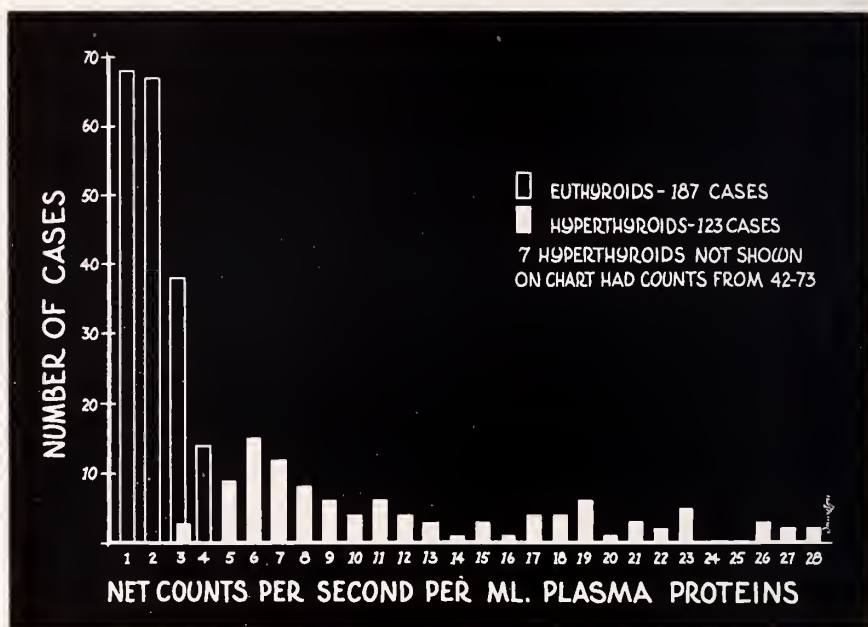


FIG. 2. Values in net counts per second of washed proteins derived from one millilitre of plasma at 72 hours after 100 microcuries carrier-free I-131 administered orally. Four counts per second is equivalent to 0.0003 microcuries I-131.

high counts in a euthyroid patient. It is perhaps, not difficult to anticipate many factors which could decrease the counts in a hyperthyroid subject but there are few if any, situations where a normal thyroid can be stimulated to the levels found in hyperthyroidism. This could occur under the influence of thyrotropin but such a situation is not likely to remain unknown to the observer.

SUMMARY

A review of the various laboratory aids in the diagnosis of hyperthyroidism has been presented. The limitations of the determination of the basal metabolic rate have been indicated and the deficiencies of the blood cholesterol as a diagnostic tool have been pointed out. The great usefulness of the protein-bound iodine content of the serum has been confirmed and its limitations noted. The newer

uses of I-131 in diagnosis employing uptake in the thyroid gland, excretion in the urine and the studies of the radioactivity of the plasma after tracer doses have been outlined and their indications and value have been presented.

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PLUMBISM IN CHILDREN

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A working knowledge of the various kinds of nuclear and cytoplasmic inclusions is of value to the pathologist as it will enable him occasionally to make a diagnosis which otherwise might be missed (Pinkerton). This dictum is valid not only for virus-caused or rickettsial and related diseases but also for problems of a toxicological nature (bismuth, lead, boron). The following example is a case in point.

CASE REPORT

History: S. J., a negro girl, aged 2 years and 9 months, was hospitalized on September 1, 1950 because of increasing lethargy, vomiting, epigastric pain and diarrhea, the latter three said to have been of two weeks duration. On admission, the child was apathetic and undernourished, with a temperature of 100°F., a pulse rate of 90 and a respiration of 40. The blood pressure was 110/68. No abnormal findings of note were encountered. A chest radiogram was unremarkable. Studies of blood and spinal fluid likewise were recorded as not abnormal.

The urine was acid with a sp. gr. of 1.030 and contained a trace of albumen as well as 3+ sugar. On the day following admission twitchings were noted with ensuing severe generalized convulsions. These occurred also on the next two days accompanied by deepening coma. The child died on the third hospital day with a hyperpyrexia of 106°F. A tentative diagnosis of encephalitis was made. The pathologist, because of a high index of suspicion for plumbism, entertained this diagnosis before performing the autopsy.

The autopsy disclosed some cerebral swelling as evidenced by gyral flattening and hippocampal grooving but no other gross findings worthy of note.

Microscopic study of the various organs disclosed small organizing thrombi in the lungs, fatty metamorphosis of the liver, gland-like changes of the outer adrenal cortex and eosinophilic nuclear inclusions in hepatic cells and those of the renal cortex and medullary rays. Many cortical renal nuclei were pyknotic with condensation of the chromatin around an inclusion body. Cytoplasmic degeneration of involved cells was also seen. Other inclusion-bearing nuclei were distorted or greatly enlarged. All these features allowed the diagnosis of plumbism to be made by examining a kidney section with the low power lens. The presence of eosinophilic inclusions in liver and kidney nuclei is characteristic of lead poisoning (Blackman).^{*} This could be corroborated by acid-fast coloring of the inclusion bodies with the Ziehl-Neelsen stain (Wachstein). Some of the pancreatic acinar cells contained one or several variably sized round, haloed, non-acid-fast bodies which only occasionally stained with eosin. A section of spine was not considered diagnostic for lead osteopathy; ribs or long bones are more suitable because of their more rapid growth. Microscopic study of the brain^{**} disclosed thickening of leptomeninges with scattered macrophages. There was edema of the white matter and widespread damage of the cortex most severe in the occipital lobes where in some sections the ganglion cells were almost completely replaced

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* We had occasion to study slides from the kidneys of an infant who succumbed to plumbism from lead ingested at the time of nursing (lead nipple shields) (Bass and Bluementhal). In this instance the inclusions are rather scant and tend to be in Henle's loops, sparing the convoluted tubules.

** We are indebted to Dr. H. M. Zimmerman for preparing and evaluating the material.

by proliferated glia. The remaining neurons were ghost-like structures. Proliferation of vessels and swelling of capillary endothelium, likewise were present. The most striking

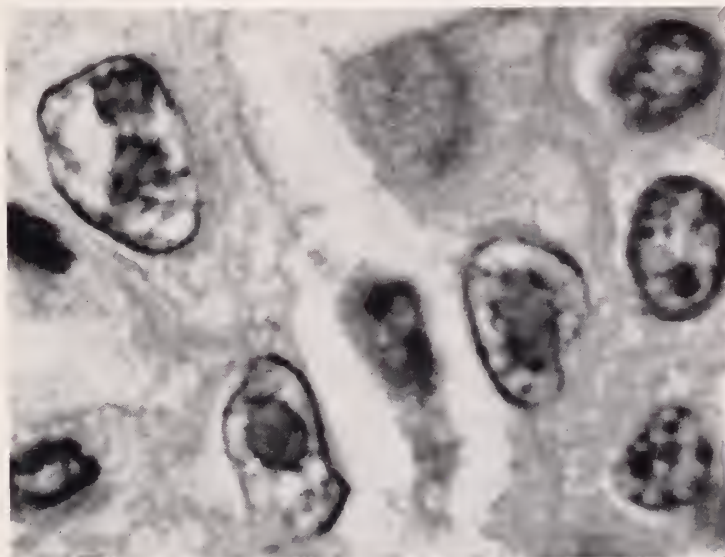


FIG. 1. Kidney; Three enlarged cortical nuclei contain oxyphilic bodies of irregular size and shape. Two inclusions are seen in the largest nucleus. All sections are stained with hematoxylin and eosin unless stated otherwise.

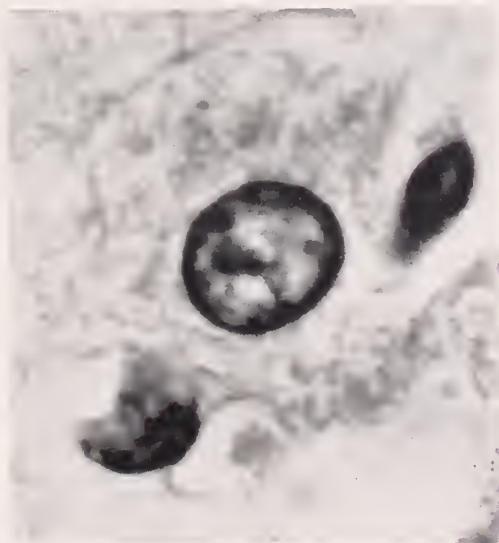


FIG. 2. Liver; a pear-shaped eosinophilic body within a hepatic cell nucleus. Inclusions of this type are acid-fast as are those in the kidney.

alterations were seen in the cerebellum, producing widespread changes visible with the naked eye in stained sections. This was caused by a serious loss in the granular and Purkinje layers. There were polymorphonuclears and macrophages with ingested basophilic

corpuscular matter as well as an increase of astrocytes and microglia, particularly in the molecular layer. These findings were interpreted as characteristic of lead encephalopathy.

After the typical acid-fast inclusion bodies were observed, a portion of formalin-fixed brain was sent to the office of the Chief Medical Examiner for chemical analysis.* This revealed the presence of 0.15 mg. per 100 gm. which is considerably above the maximum normal of 0.09 mg. (1).

*Additional information obtained on reporting the case to the Department of Health:*** Three months before her final illness the child was noted to be ill with swollen and painful gums. A dentist at another hospital diagnosed this as a vitamin deficiency. At about this

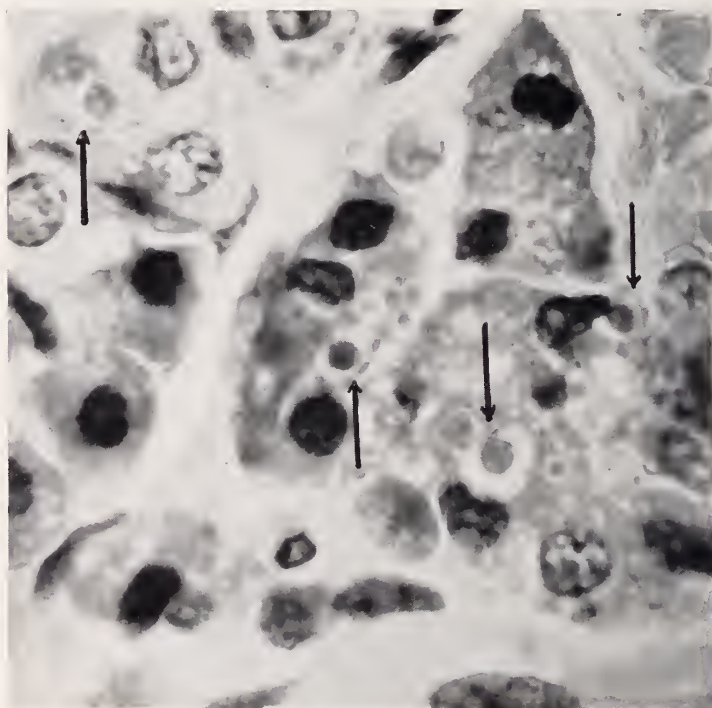


FIG. 3. Pancreas; numerous spherical cytoplasmic bodies surrounded by haloes (arrow). They resemble inclusions described in boric acid poisoning (Fisher) but are for the most part not oxyphilic, neither are they acid-fast. Similar inclusions in the liver were seen by Terbrüggen and by Pappenheimer and Hawthorne in routine autopsy material.

time the mother noted a dark line at the gum margin of the upper incisors. The child was given penicillin without effect. The existing anorexia continued and led to weight loss. Periods of lethargy (late sleeping in the morning) occurred as well as bouts of irritability and screaming attacks at night. The day before admission she was seen in the outpatient department several times for vomiting and increasing lethargy.

Questioning of the mother after establishment of the autopsy diagnosis disclosed that

* We are indebted to Dr. A. O. Gettler for the toxicological study. The amount of lead stored in various organs in protracted saturnism decreases in the order of enumeration: long bones, short bones, liver, kidney, brain (1).

** Our thanks are due to Drs. H. Lubenstein and M. Greenberg of the Bureau of Preventable Diseases.



FIG. 4. Cerebellum; extensive destruction of the granular layer. Celloidin, Nissl

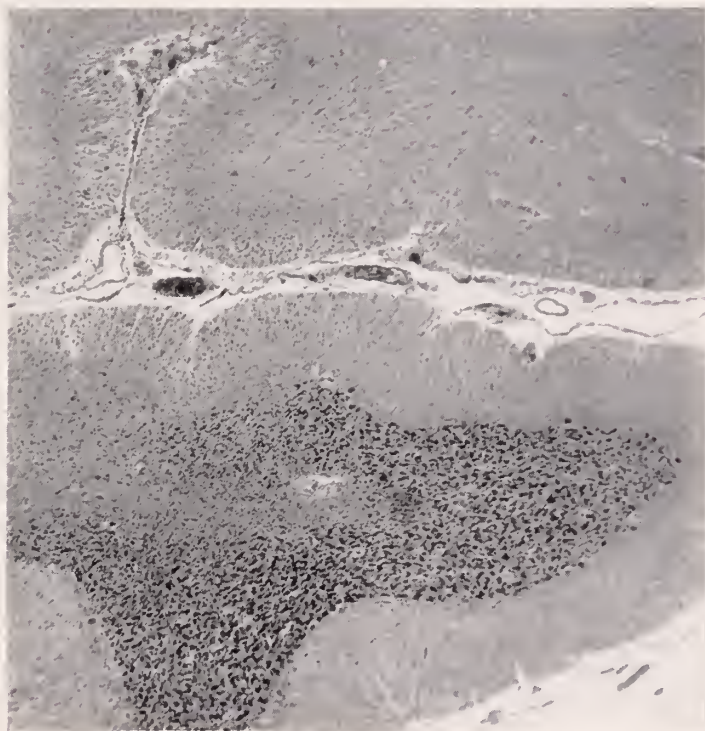


FIG. 5. Where the granular layer has disappeared, there is atrophy of the molecular layer and gliosis.

for one year prior to death, the child had been a severe feeding problem. In addition, she developed the habit of eating paint and plaster from the walls of the bathroom which were defectively painted and chipped in many places.

DISCUSSION

Concerning the true incidence of fatal plumbism in children it may be safely said that until a few years ago many more cases were missed than diagnosed. This fact emerges from a study of the mortality figures for the 10-year period of 1931-1940 in which of 202 children dead of plumbism throughout the country 49 (24.3%) alone were reported from Baltimore. This can only be explained by failure of making the diagnosis in many instances elsewhere (MacDonald and Kaplan).^{*} The recent decrease in diagnosed cases in this country can be ascribed to the ban imposed on lead containing paints for furniture, toys etc.

Chronic lead poisoning in childhood may be arbitrarily divided into three age groups (Burrows et al.). In infants lead nipple shields are the most common sources of poisoning in this country while children of preschool age are victims of pica as was our case. Older children are exposed to a greater variety of hazards similar to adults (e.g., inhalation of fumes from burning battery casings used as fuel).

From a knowledge of the mortality and permanent morbidity of the severer forms of lead encephalopathy it appears unlikely that the life or the cerebral integrity of the patient could have been saved. The problem that cases of this severity pose is therefore largely an academic one. The following points, however, could have aided in establishing the diagnosis. Vomiting, abdominal pain and constipation or diarrhea should be sufficient reason to question the mother for the presence of pica and to examine radiologically the abdomen, thorax and the long bones for ingested radio-opaque material and osseous lead lines in ribs and extremities respectively. Thus needless laparotomies may be avoided.

After the onset of encephalopathy (stupor, twitchings, convulsions) glycosuria and acetonuria may appear in addition to the above mentioned picture of an acute abdomen. This necessitates differentiation from diabetes mellitus or uremia and from encephalitis, tuberculous meningitis and cerebral neoplasm. Glycosuria (present in our case) is thought to be of renal origin and thus unaccompanied by hyperglycemia. There is no polyuria in plumbism.

Involvement of cranial or peripheral nerves will have to be differentiated from poliomyelitis and peripheral neuritis due to other causes.

Of the various procedures which aid in establishing a diagnosis radiography of abdomen, thorax and long bones is of great value, as it combines ready availability with a high specificity. It should be used more often in the differential diagnosis of the above named conditions in infancy and childhood. Chemical examinations of urine and blood although desirable are time consuming and frequently unavailable. However, increased excretion of coproporphyrin type III in the urine

^{*} Only two instances of fatal saturnism in children were reported to the Department of Health of New York City in the year 1950, one of these is the case under discussion. (Personal communication of Dr. M. Greenberg, Bureau of Preventable Diseases.)

which is a typical feature of plumbism may readily be detected (4). Punctate basophilia with anemia or a lead line of the gums may cause the alert technician or dentist to be the first to suspect plumbism, just as nuclear inclusions in kidney and liver may give the clue to a puzzling case (Wachstein).

From the standpoint of the pathologist there is very little that will have to be considered in the differential diagnosis. Nuclear inclusions are found in the kidney in so-called "inclusion body disease," in occasional cases of virus encephalitis and in bismuth medication. The first disorder produces marked cellular enlargement as well as involvement of numerous other organs, while encephalitic inclusions in the kidney tend to be extremely scant. The Ziehl-Neelsen stain will be helpful as it will single out inclusions caused by lead and bismuth (Wachstein). Bismuth inclusions, however, are somewhat brownish, more refractile and spare the liver. They give a characteristic orange-colored reaction when treated with a special reagent (Wachstein and Zak).^{*} A negative history for bismuth medication and chemical determination revealing significant levels for lead will be sufficient to establish the diagnosis even in the absence of permission to examine the brain or in cases where there was no cerebral involvement or where non-fatal plumbism is an incidental finding diagnosed under the microscope. A discussion of the current forms of treatment is beyond the scope of this paper and may be found in a recent review (Burrows et al.).

SUMMARY

A fatal case of lead encephalopathy in a child with pica is presented. The diagnosis was unsuspected clinically and based on the presence of acid-fast nuclear inclusion bodies in kidney and liver. Typical microscopic changes of the brain and a significant increase of lead in this organ corroborated this.

The differential diagnoses are discussed from the standpoints of the clinician and the pathologist.

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^{*} Whether altered renal cells appear in the urinary sediment comparable to those seen during bismuth medication (for literature see Wachstein and Zak) remains to be seen.

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ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out patient department of the Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

Cushing's Syndrome Due to Tumor of Adrenal Cortex. H. M. GOLDSTEIN. *Am. J. Dis. Child.*, 78: 230, August, 1949.

A case of Cushing's syndrome in an 11 month old infant with onset at 3 months with apparent surgical cure following the removal of a tumor of the right adrenal cortex is described. This syndrome is differentiated from the adrenogenital syndrome because of varied symptomatology, therapy, course, prognosis. The diagnostic importance of determination of the urinary excretion of 17-ketosteroids and of special roentgenographic methods is emphasized. A pre- and postoperative regimen of hormone and fluid therapy is outlined for the management of such cases.

Streptomycin in the Treatment of Whooping Cough. LEWIS WANAMAKER, J. L. KOHN, AND M. WEICHSEL. *Am. J. Dis. Child.*, 78: 201, August, 1949.

Streptomycin was administered to 129 patients, of whom 100 were under 1 year of age. A large majority of the children were admitted during the first week of the paroxysmal stage. They came from a poor economic background and very few had been given any prophylactic whooping cough vaccine injections. The patients were divided into 4 main groups: streptomycin was administered (1) by intranasal drops to 52 children; (2) by aerosol mist to 35 children; (3) by intramuscular injection to 26 children; (4) a combination of aerosol and intramuscular injection to 12 patients and by another combination to 4 patients. The severity of the illness was often a factor in the choice of the treatment. There was a group of 31 children who received no streptomycin. When given by the intranasal route streptomycin had no therapeutic value. When given by aerosol or intramuscular injection, there was a favorable influence on the course of the whooping cough in most of the children. About 68 per cent of all the children were moderately ill on admission and the course of the illness in this group was favorable in 75 per cent and a failure in only 5 per cent. The course of those children who were moderately ill and received no streptomycin was less favorable. About 21 per cent of the children were severely ill on admission and the course of the illness was favorable in about 60 per cent and a failure in about 20 per cent. There were 5 deaths in this latter group. The dosage for aerosol administration was 50 mg. of streptomycin dissolved in 1 ml. of normal saline given 3 times daily for 5 days, after aspiration of excessive mucous from the nose and mouth. In young children the aerosol was administered under a plastic hood. The dosage for intramuscular injection up to 1 year was 500 mg. per day divided into 8 equal doses for 5 days; up to 3 years of age 800 mg. per day for 5 days. Up to the present the factor of resistance of *H. pertussis* to streptomycin has not become a problem in the treatment of whooping cough. The treatment of streptomycin seemed to have no effect on the presence of *H. pertussis* in the nasopharynx.

Prolapsed Gastric Mucosa: A Possible Cause of "Gastric" Symptoms in Right Heart Failure. M. MELAMED AND A. MELAMED. *Ann. Int. Med.*, 31: 245, August, 1949.

Four cases of right heart failure in which redundancy of the prepyloric rugae of the stomach was found are reported. In all of these patients gastrointestinal symptoms were

present. It is believed that the pathologic changes in "congestive gastritis," at least in some cases of right heart failure, predispose to prolapse of the gastric mucosa. That prolapse of the gastric mucosa can cause symptoms cannot be denied. There seems to be a definite correlation between right heart failure and "gastric" symptoms in such right heart failure. Since cardiac decompensation is reversible in many cases, so might prolapsed gastric mucosa be where the basis for its presence can be attributed to congestion of the peripheral circulation.

A Simple and Efficient Cataract Suture. J. LAVAL. Arch. Ophth., 42: 189, August, 1949.

A conjunctival incision is made 5 mm. from the limbus for one-half the circumference of the cornea. The conjunctiva is undermined to the limbus and the corneoscleral junction is exposed in the region of 12 o'clock. A keratome incision about 5 mm. long is made at this point. One needle of a double-armed suture (000000 silk with arc atraumatic needle) is passed through the outer layers of the scleral lip of the keratome wound, the point of the needle facing the surgeon. The other needle of the double-armed suture is passed through the corneal lip of the keratome wound, the needle tip facing away from the surgeon. The first needle, which passed through the scleral lip, is now taken through the conjunctiva close to its attachment to the corneal lip, the tip of the needle facing away from the surgeon. The suture is looped away from the wound and a loose tie taken. The section is enlarged with scissors. A peripheral or a complete iridectomy is performed, the lens is removed, and then the suture is firmly tied, the corneal and the scleral edges of the wound being brought snugly together. The conjunctival incision is closed by a running silk suture (000000), with a knot tied firmly at each end of the suture. This gives good tight conjunctival closure.

Adenoma of the Bronchus: Endoscopic Treatment in Selected Cases. M. L. SOM. J. Thoracic Surg., 18: 462, August, 1949.

Fifty cases of endoscopically proved adenoma of the bronchus were reviewed. Fifteen, or 30 per cent, of these remained completely cured or symptom-free following bronchoscopic removal, usually with coagulation of base. Pedunculated smooth globular tumors originating in the main bronchi seem most suitable for endoscopic removal provided the diagnosis is established early. Tumors situated in the branch bronchi are distinctly not favorable, both because they are less accessible and show a tendency to spread intramurally. The persistence of the tumor as suggested by bronchial wall involvement, a persistent roentgen shadow, or a consistently positive biopsy suggests extrabronchial spread and requires surgical removal. With the development of a relatively safe technique for the removal of a lung lobe, extrabronchial adenomas are now being treated in this manner with increasing frequency.

Traumatic Coronary Thrombosis with Myocardial Infarction. H. LEVY. Arch. Int. Med., 84: 261, August, 1949.

A rare instance of thrombosis of a major coronary artery, with consequent myocardial infarction due to contusion of the wall of the chest, is described. A woman of 50 years with previous hypertension was thrown forcibly against the seat of a car in an automobile accident and complained of immediate chest pain. There was classical electrocardiographic evidence of coronary thrombosis with myocardial infarction. Sudden death occurred on the 13th day. Post-mortem findings corroborated the age of the lesion.

The Cold Permanent Hair-Waving Process. A Dermatologic and Clinical Study. H. T. BEHRMAN, F. C. COMBES, G. WEISSBERG, AND M. G. MULINOS. J. A. M. A., 140: 1208, August, 1949.

This report concerns the effects of certain cold wave lotions on the health of 1,200 persons who volunteered for tests of these products. Many of them included normal persons and some with various skin diseases; persons without any known contact with cold waving lotions, as well as a great number subject to prolonged previous contact. Patch tests were

employed in the evaluation of cutaneous irritation and sensitization. The test materials included commercial cold waving lotion, fresh and shelf-aged for a year; a 2 per cent solution of potassium bromate (neutralizer); a mixture of lotion and neutralizer in varying proportions, and solutions of ammonium thiglycolate at *ph* 9.2 and concentrations of 0.5, 1.0 and 1.5 normal for the determination of primary irritation. By the use of adequate numbers of paired patch tests on subjects with (a) no known previous contact with the cold waving solutions, and (b) varying contact with the solutions; by the retesting of each subject within 2 to 4 weeks, and by interpreting the results in conjunction with a large body of data obtained under conditions of actual use, it was shown that these solutions have a low degree of irritancy, even when used in concentrations triple that used in practice. On the basis of these studies, cold wave preparations used in this investigation exhibited a low level of cutaneous irritation and in the literature attention has been directed to toxic manifestations, primarily, of a hepatotoxic nature, resulting from the use of cold wave preparations. Careful and intensive studies of a clinical and laboratory nature do not support the contention that toxic manifestations result from the use of cold wave preparations. Evidence of systemic toxicity from frequent exposures to cold waving solutions tested was not found.

Progress in our Pharmacological Knowledge of Drug Action. E. P. PICK. Wein. Klin. Wchnschr., 61: 1, September, 1949.

On the occasion of the 10th anniversary of the passing of Hans Horst Meyer, one of the founders of modern experimental pharmacology, an attempt is made to describe some of the rapid advances in the theory of drug action on the cells during the past 10 years. This is largely established by the selective action of various newly detected hormones, vitamins, and antibiotics on the enzymatic processes in different organs and cell complexes, and on the vegetative nervous system. Knowledge of the chemical metabolism of the living organism has recently been advanced by the use of radioactive isotopes. The "dynamic" state has been shown in the ease with which many drugs pass through tissues and cell membranes, often against osmotic pressure and other physico-chemical barriers. It is therefore not probable that surface tension of cells alone is of paramount importance for drug action; it seems that solubility in cell lipoids and changes of permeability in the cell-lipoid-membranes are very important factors in the pharmacological and biological effect of drugs in general, and especially for the specific activity of narcotics and hypnotics. The experimental approach shows, however, that drug action is a complex process involving selective action on the various cell receptors and enzymes in the boundary cell-membranes and in the cell-protoplasm. For instance, the inhibition of sugar absorption in the intestines of phloridzin-poisoned animals is clearly explained by the action of the drugs in inhibiting the dehydrogenase-enzymes needed for sugar-phosphorylation which precedes absorption. This is an example of the blocking of enzymatic reaction very important for biological action. Other examples are: the action of parasympathetic drugs in inhibiting cholinesterase, and the effect of sympathetic agents, such as ephedrine or cocaine, which by checking amino- and phenol-oxidases prevent the destruction of adrenalin. The greatest achievements in the knowledge of drug action were obtained by studies of various glands of internal secretion, especially of the anterior part of the hypophysis and its various relations to the hypothalamus, adrenal cortex, thyroid, pancreas, and sex glands. The action of the adrenocortical hormone, Cortisone, in regulating the metabolism of collagen tissues, the effect of thyrotropic hormone in stimulating thyroxin production, the influence of thiouracyl and its derivatives and of isotope iodine on the overactive thyroid are not only new important achievements in biological cell research but also are representative of the very valuable medicaments developed in the course of these studies. Another interesting finding is the diabetogenic effect produced by the anterior part of the pituitary gland which lead to the explanation of the sensitizing insulin-action on hexokinase, an enzyme produced by the anterior pituitary which performs the phosphorylation needed before hydrolysis of glucose. We should also mention the biological importance of different protein-split prod-

ucts, mostly known as "essential" amino acids, for the production of vital cell catalysts; they are required for the production of plasma proteins, as well as for the formation of insulin, adrenaline, the antipellagra vitamin, nicotinic acid, and many other vital materials. The study of the relationship between growth-enzymes for microorganisms and the vitamins which led to the discovery of substances such as pyridoxine, folic acid and the antipernicious vitamin, B₁₂, belongs among the most important achievements in theoretical and practical medical science. Studies on the sulfa drugs and antibiotics have shown that these drugs influence some of the oxidative enzyme reactions most important for the nutrition and growth of the infecting microorganism without disturbing the cell metabolism of the host; this is in contrast with the old disinfectants which destroyed the cell proteins of the microorganisms. The discovery of the antagonistic relationship between sulfanilamide and para-aminobenzoic acid led to the generally accepted hypothesis, that the competition between structurally related compounds is the explanation for the bacteriostatic action of the sulfonamides. This new concept of competitive displacement holds also for many other pharmacological reactions. A great advance in the knowledge of the pharmacology of the vegetative nervous system has been presented by the new sympatholytic drugs, Dioxane derivatives, Priscol, and Dibenamine. These compounds antagonize adrenalin-action in cases of essential high blood pressure (pheochromocytomas). The detection of the secretion of nor-adrenalin as a second sympathetic body hormone and its presence in considerable amounts in pheochromocytomas and various other tissues has opened a number of new important questions. Related to the sympatholytic substances are the antagonists of histamine, e.g., Antergan, Benadryl, Pyribenzamine and others. It is striking that some of these antihistamine and antiallergic drugs have not only a peripheral effect but also act as hypnotics and sedatives and show excellent action against nausea, vomiting, vertigo, e.g., in Parkinson's disease. This brief and by far incomplete survey of the progress in pharmacology in the last 10 years may support the idea of H. H. Meyer, that rational drug therapy must be established on experimentally obtained knowledge of cell metabolism; the few examples may show that our understanding of drug action is dependent on our knowledge of the enzyme systems functioning in the animal cell under physiological and pathological conditions.

Procedure for Determination of Aerosol Delivery and Stability During Nebulization. H. A. ABRAMSON, B. SKLAROFKY, AND C. REITER. *Ann. Allergy*, 7: 612, September/October, 1949.

A centrifugal coil which efficiently condenses aerosols produced by commonly used nebulizers is described. The effects of volume velocity, initial concentration, and viscosity of the liquid in the nebulizer, on delivery by the nebulizer, are discussed on the basis of quantitative data. It is shown by this procedure that sodium ascorbate aerosol, nebulized by oxygen, is comparatively stable, provided sufficiently high concentrations are employed. Suggestions for the clinical application of these results are provided which demonstrate how time of therapy may be shortened, with a marked increase of the material delivered by the nebulizer.

Roentgen Therapy for Pituitary Adenoma. A. L. BACHMAN AND W. HARRIS. *Radiology*, 53: 331, September, 1949.

The results of radiation therapy in 64 cases are presented. Distinct improvement was obtained in 58 per cent of 38 cases of chromophobic adenoma, 43 per cent of 21 cases of eosinophilic adenoma, and 4 out of 5 cases of basophilic adenoma. The results of multiple course therapy were compared with those of single course therapy. On the average, the latter resulted in earlier benefit with lower total dosage provided an adequate amount of radiation was given during the single series. Microscopic sections were available in 16 cases which had received radiotherapy. In no case was there complete destruction of the tumor by radiation. The evidence indicates that while pituitary adenoma is practically never destroyed by roentgen rays, its size is definitely decreased and its growth potentiality con-

siderably diminished in a large percentage of cases. At present, optimal therapy is the initial administration of 3000 r to 4000 r tumor doses in 30 to 45 days for a case of average severity. If no early satisfactory improvement occurs, surgical intervention is indicated. No satisfactory result usually can be expected from additional radiotherapy if the above dosage fails. However, if the first series results in considerable improvement and is then followed by recurrence, at least some success may be expected from a second course.

The Increased Hypoprothrombinemic Effect of a Small Dose of Dicumarol in Congestive Heart Failure. D. STATS. Am. J. M. Sc., 218: 318, September, 1949.

The hypoprothrombinemic effect of a single dose of 150 mg. of dicumarol was determined in 48 control subjects and in 36 patients with varying degrees of right-sided cardiac failure. Clinical and statistical analysis of the results showed an increased response in those cardiacs with moderate to severe failure. When dicumarol is administered to patients in cardiac failure for the treatment of thromboembolic conditions, doses smaller than those recommended for the average patient should be administered.

Therapeutic Results in Advanced Chronic Simple Glaucoma with Telescopic Fields. S. BLOOMFIELD AND L. KELLERMAN. Am. J. Ophth., 32: 1177, September, 1949.

A study was made of the treatment of 41 eyes with uncontrolled chronic simple glaucoma sufficiently advanced to produce a constriction of central fields to 10 degrees from fixation. In 19 of these eyes, surgery was performed to reduce the tension, with subsequent loss of some visual acuity in 84 per cent of the cases, and a reduction in acuity to less than 20/200 in 47 per cent, over a follow-up period averaging a little over 2 years. In the remaining 22 eyes, the tension remained above normal range but no surgery was performed. In this group, over a comparable period, some visual loss occurred in 36 per cent, and an extreme reduction in acuity to less than 20/200 in 14 per cent. These facts suggest that in eyes with advanced chronic simple glaucoma of this degree, central vision may be retained for long periods in spite of inadequately controlled tension, and that in such cases operation to reduce the tension is contraindicated.

Collapse of the Vertebral Bodies in Sickie Cell Anemia. W. A. HENKIN. Am. J. Roentgenol., 62: 395, September, 1949.

Two cases of sickle cell anemia, one in a Negro boy, aged 14, with osteoporotic collapse of the thoracic and lumbar vertebral bodies and the other in a Negro girl, aged 12½, with similar changes in the lumbar vertebral bodies are presented. This is believed to be the first report of this finding in children. In sickle cell anemia hemolysis of abnormal erythrocytes is followed by an intense erythropoietic reaction in the bone marrow with congestion, infarction and connective tissue replacement of cancellous bone. Coarsening of the trabecular structure is evidence of osteoblastic reaction in the weakened bone. The thoracic and lumbar vertebral bodies, composed of cancellous bone and subject to great stresses, may show a gradual reduction in height. Similar changes occur in Paget's disease (osteitis deformans). In senile osteoporotic collapse of the vertebral bodies there is no roentgenographic evidence of osteoblastic activity. Polycythemia vera, a disease in which hemorrhage and thrombosis are common complication, shows no bone changes similar to those found in sickle cell anemia; nor are such changes seen in Cooley's anemia or congenital hemolytic anemia.

Longevity of Schistosoma Mansonii; Observations Based on a Case. R. S. WALLERSTEIN. Am. J. Trop. Med., 29: 717, September, 1949.

A case of Schistosoma mansonii infestation is reported in a 32 year old Puerto Rican woman, who had been out of the endemic area and a resident of New York City for 26 years. Evidence was adduced that this patient had living adult flukes in her body alive at least 26 years, an extension of the known life span of this parasite. Review of the litera-

ture reveals that *S. hematobium* has been known to have an equal longevity and that the same has been reported with *S. japonicum* but not as well as can be determined, ever before with *S. mansoni*. The association of polypoid schistosome granuloma with possible malignant transformation is again noted.

The Relationship of Chronic Recurrent Sialadenitis to the Alarm Reaction. H. E. BASS, AND M. MENDLOWITZ. *Ann. Otol. Rhin. & Laryng.*, 58: 868, September, 1949.

Recurrent sialadenitis has been attributed to allergic or infectious factors by most authors, although 2 observers have noted a high incidence of psychoneurosis in such patients. Experimental work has shown that the parotid glands participate in the alarm reaction. Two cases of recurrent sialadenitis are presented in which no allergic or infectious factors could be demonstrated. The sialadenitis in the cases presented in this paper was found in emotionally unstable individuals subjected to severe social and environmental stress. It is possible that these cases represent manifestations of the alarm reaction.

Studies on Serum Carotene in Man. D. ADLERSBERG, S. KANN, A. MAURER, K. NEWERLY, V. WINTERITZ AND H. SOBOTKA. *Am. J. Digest. Dis. & Nutrition*, 16: 334, September, 1949.

A carotene tolerance test employing 120 mg. of crystalline carotene in a vehicle of 24 gm. of butter was elaborated for the study of carotene metabolism in man. A test dose of 60 mg. carotene in 12 gm. of butter proved too small, while the higher dose of 180 mg. carotene in 36 gm. of butter offered no additional advantage. The elevation of the serum level of carotene under these conditions is relatively smaller and occurs at a slower rate than that of Vitamin A in oil in analogous absorption tests. Bile acids moderately accelerated the absorption of the carotene from cottonseed oil, while lecithin caused pronounced acceleration and intensification of absorption. Cottonseed oil was inferior to butter as a vehicle. It is suggested that the superiority of butter as a carotene vehicle is due to its high lecithin content. Complete lack of carotene absorption from butter was observed in severe hepatic damage. Normal function of the liver is essential for absorption of carotene in man.

Chorda Tympani Nerve Graft. SAMUEL ROSEN. *Arch. Otolaryng.*, 50: 243, September, 1949.

The author describes the use of a living pedicle graft to cover the fenestra for the first time in fenestration surgery. This graft consists of the chorda tympani nerve. The immediate post-operative effect is a quicker return of hearing and a higher level of improvement than that achieved with the standard technique. These results have been maintained after a one-year follow-up. Available evidence suggests that patients with disabling otosclerosis should not be discouraged from seeking surgical relief. Non-surgical treatment is of little benefit.

Contact Allergic Dermatitis due to the Procaine Fraction of Procaine Penicillin. S. M. PECK AND F. F. FELDMAN. *J. Invest. Dermat.*, 13: 109, September, 1949.

This is the first report of a patient who developed a sensitivity to the procaine—and not to the penicillin—from contact with procaine penicillin. In addition, the patient showed concomitant cross-sensitization to related and unrelated chemicals such as sulfathiazole, paraphenylenediamine, para-aminobenzoic acid, various local anesthetics and ammoniated mercury. Since sensitivity developed only to procaine and not to penicillin itself, it is speculated that a very weak linkage must exist in the procaine penicillin molecule.

Studies of Sweating. 11. On the Mechanism of Action of Local Antiperspirants. MARION B. SULZBERGER, FREDERICK G. ZAK, AND FRANZ HERMANN. *Arch. Dermat. & Syph.*, 90: 404, September, 1949.

Serial sections of 12 biopsy specimens from the axillary skin of healthy volunteers were studied after application of 2 antiperspirant preparations containing aluminum sulfate as

the active ingredient. The entis showed distinct reactive alterations, more pronounced after application of the more effective preparation, and absent in the control specimens. In the eccrine sweat glands there was considerable cellular infiltration through the epithelium of the perpendicular portion of the ducts, together with perivascular cuffing in the upper corium. Many of the apocrine sweat glands showed degenerative alterations of the lining of a great part of the acini (tubules), with conspicuous desquamation of epithelial cells and formation of cellular casts. These changes may well participate in the mechanism of antiperspirant action. There was no narrowing or collapse of the ostiums of the ducts of either eccrine or apocrine glands.

Psychiatric Observations Concerning Rhinoplasty. L. LINN, AND I. B. GOLDMAN. *Psychosom. Med.*, 11: 307, September/October, 1949.

This report is based on a psychiatric study of 58 rhinoplasty patients. With few exceptions the patients who presented themselves for rhinoplasty were ill from a psychiatric point of view. This illness varied from minor neurotic disturbances to overt schizophrenic psychoses. Along with the basic psychiatric disorder there was present a special group of symptoms designated as the "syndrome of the rhinoplasty patient." As a result of excessive self-consciousness relating to the nose, these patients become constricted in their bodily movements, in their dress, in the flow of their attention, in their ability to relate warmly to other people and in their capacity to concentrate on their work. In the immediate reaction to rhinoplasty a temporary period of marked psychiatric improvement frequently occurs. This is followed by a varying degree of relapse. However, fundamental changes of a beneficial character frequently persist. The theoretical basis for the observed psychological changes is presented in terms of Schilder's "body-image" concept. The special significance of the nose in the structure of the "body-image" is discussed. The psychological changes following plastic surgery are contrasted with those seen as magical effects following other surgical procedures. Contrary to general opinion rhinoplasty is not a hazardous procedure from a psychiatric standpoint. Many patients will require deep and prolonged psychotherapy in addition to the rhinoplasty to achieve maximal happiness and effectiveness.

Histological Study of the Destruction and Regeneration of the Gastric Mucous Barrier Following Application of Eugenol. Preliminary Report. F. HOLLANDER AND R. H. GOLDFISCHER. *J.N.C.I.*, 10: 339, October, 1949.

Changes in the gastric mucous barrier after repeated application of a mucigogue-desquamatory agent to the mucosa of dogs' Heidenhain pouches are discussed. The experimental results show that successive applications of eugenol emulsion effect a progressive removal of columnar cells from the mucosal surface and from the crypts, until the connective tissue matrix containing the collecting tubules of the glands is exposed. The regenerative process can be divided into three stages: (1) Preliminary resurfacing of denuded mucosa with flat and fusiform-shaped cells, evident as early as 30-60 minutes after removal of eugenol from the pouch; (2) transformation of these new cells into columnar cells; and (3) reformation of crypts. This entire regenerative process has been found to occur within 36 hours following mucosal impairment. The surprising rapidity with which these changes take place serves to explain many aspects of the previous study from this laboratory on the changes in microscopic and physicochemical character of the mucous secretion collected after similar treatment. The results indicate the conditions of pretreatment of the gastric mucosa which may be suitable for attempts at gastric carcinogenesis.

Sigmoidorectal Electrosurgical Snare. R. TURELL. *New York State J. Med.*, 48: 2311, October, 1949.

A new type of high frequency snare is described and illustrated. It is recommended primarily for the removal of pedunculated new growths of the rectum and the lower sigmoid.

Guided Liver Biopsy through Laparotomy Incision. E. E. JEMERIN. N. Y. State J. Med., 48: 2276, October, 1948.

A method is discussed whereby a selective liver biopsy may be obtained once the abdomen has been opened, even though the abdominal incision is too far distant for direct biopsy under vision. This is effected by guiding into a palpable liver lesion an aspirating needle introduced through the upper abdominal or lower chest wall, a hand inserted into the abdomen through the original incision serving as the guide. Such a procedure may be found useful on various occasions that palpatory findings are not clear and are inaccessible for direct sampling. Definitive sampling can be accomplished with relative assurance in this manner. A case is reported in which the presence of a single, tiny metastatic nodule was verified through a primary incision in the left lower quadrant for a carcinoma of the rectosigmoid. The prognosis and procedure for the primary lesion were modified accordingly.

Vitamin E in Arteriosclerotic Heart Disease with Electrocardiographic Evidence. M. E. EISEN AND H. GROSS. New York State J. Med., 49: 2422, October, 1949.

Vitamin E, containing 50 mgms. alpha tocopherol gelscals in doses ranging from 150 to 800 mgms. daily given over a period of 1 year, was found to produce no beneficial effect in subjective or objective symptoms when given to 16 cases of arteriosclerotic heart disease, 5 cases of arteriosclerotic heart disease with congestive failure, 2 cases of luetic heart disease, 12 cases of arteriosclerotic peripheral vascular disease and 2 cases of thromboangitis obliterans. Exercise tolerance tests prior and subsequent to Vitamin E therapy were performed and no beneficial changes were produced. Electrocardiograms were taken following the administration of placebos and massive doses of Vitamin E before and after exercise. In the cases of heart disease, peripheral vascular disease or a combination of both, the electrocardiograms either no change or further impairment following Vitamin E in the period of 1 year.

Some Clinical Applications of Electrokymography. The Findings in Myocardial Infarction and Heart Block. M. L. SUSSMAN, S. DACK, AND D. H. PALEY. Radiology, 53: 500, October, 1949.

The use of elektokymography in clinical diagnosis is reviewed briefly. Clinical application is illustrated by an analysis of 3 cases of coronary thrombosis with myocardial infarction. The elektokymograms in these cases showed a normal pattern over the upper left ventricular border. In the lower ventricle there was delay in the onset of contraction followed by retarded systolic mesial movement. In 2 of the cases there was frank systolic expansion and paradoxical movement in the rapid inflow phase of diastole. With rare exceptions such findings indicate antecedent myocardial infarction or ventricular aneurysm. The physiological potentialities of this method of analysis of the events in the cardiac cycle are considered through a description of the findings in 2 cases of complete heart block.

Intracellular Bile Canaliculi in the Rabbit Liver. (17391). M. WACHSTEIN. Proc. Soc. Exper. Biol. & Med., 72: 234, October, 1949.

With the aid of the histochemical phosphates stain, intracellular bile canaliculi can be demonstrated in the normal rabbit liver. These intracellular branches become considerably more pronounced following experimental biliary obstruction.

Roentgen Examination of the Hip in Legg-Perthes' Disease. S. SIFFERT AND E. H. BETTMAN. Radiology, 53: 548, October, 1949.

Over forty cases of Legg-Perthes' Disease were studied from the roentgenological standpoint in an attempt to establish a routine for examination that would preclude overlooking defects in the femoral capital epiphysis. A four-plane routine was considered most satisfactory, so that any single lesion that was clearly demonstrated in any one of the four views, could be followed accurately in that plane. Studies using an anatomical specimen

from the upper femur that had been cut into four quadrants, revealed that x-rays could be taken in various planes so that the absence of a full quadrant could not be discerned. This possibility cannot occur with the four-plane technique.

Acute Coronary Insufficiency Due to Pulmonary Embolism. S. DACK, A. M. MASTER, H. HORN, A. GRISHMAN, AND L. E. FIELD. *Am. J. Med.* 7: 464, October, 1949.

A study of 41 consecutive fatal cases of pulmonary embolism confirmed by autopsy showed that acute coronary insufficiency is an important factor in determining the electrocardiographic and myocardial effects following embolism of the pulmonary artery. The electrocardiographic pattern of "acute cor pulmonale" (deep S1 and Q3, depressed RS-T in Lead 1, elevated RS-T in lead 111 and T3 inversion) occurred in only a minority of cases. In the majority the electrocardiographic changes were those characteristic of acute coronary insufficiency, namely, RS-T depression and T wave inversion in one or more leads and often in all leads. Antecedent hypertensive or arteriosclerotic heart disease and cardiac hypertrophy were important predisposing factors of acute coronary insufficiency. The classical cor pulmonale pattern was seen more often in patients with previously normal hearts. Changes indicative of myocardial necrosis or infarction resulting from acute coronary insufficiency were found in 10 cases or 24 per cent. In 3 of these cases there were gross changes in the myocardium and in 7 cases histologic changes. Acute occlusion of a coronary artery was not seen in any of the hearts. The most frequent sites of necrosis were the sub-endocardial layer of the left ventricle and the papillary muscles. Coronary insufficiency following embolism of the pulmonary artery is caused by diminished coronary blood flow and myocardial anoxia which result from systemic shock, right ventricular dilatation, anoxemia and possible reflex vasoconstriction.

Reduction of Potassium Tellurite by Living Tissue (17369). M. WACHSTEIN. *Proc. Soc. Exper. Biol. & Med.*, 72: 175, October, 1949.

Reducing activity in living tissue can be demonstrated with the aid of potassium tellurite. Under the microscope, the sites of reduction are indicated by insoluble dark tellurium. Various bacteria, including strictly anaerobic ones as well as yeast and leucocytes from human material, reduced potassium tellurite. Among different mammalian tissue examined, kidney gave the most constant result, permitting histochemical localization in certain portions of the nephron. Active SH groups apparently are essential for the reduction of potassium tellurite by living tissues.

Encephalopathy Following Pertussis Vaccine Prophylaxis. J. H. GLOBUS AND J. L. KOHN. *J. A. M. A.*, 141: 507, October, 1949.

Two cases are described in which manifestations of cerebral involvement followed inoculation with pertussis vaccine. In 1 instance the reaction was at least partly reversible, but in the other there was a fatal termination. In the latter instance, postmortem investigation revealed anatomic changes of a diffuse, primary, degenerative nature in the brain. These histologic features, non-inflammatory in character, suggest the probability that an allergic form of encephalopathy was caused by an antigen-antibody reaction.

Newer Advances in Gout. D. ADLERSBERG. *Bull. New York Acad. Med.*, 25: 651, October, 1949.

The first part deals with the status of uric acid in the blood (uric acid partition). Ultrafiltration of blood serum was used for separation of "free" and "bound" uric acid. Comparatively constant uric acid partition is characteristic of the normal individual, the bound uric acid representing 16 per cent (range 4-24 per cent) of the total uric acid of the serum. In pathologic conditions, gout and hepatic damage bring about disturbance of uric acid partition, diminution of the free and elevation of the protein bound fraction. The second part discusses hereditary hyperuricemia and its relation to hereditary hypercholesterolemia. Twenty-seven members of families with hereditary hypercholesterolemia, whose

cholesterol levels ranged 250-870 mg. per 100 cc., average 452 mg., were studied for uric acid content of blood serum. One-third had levels above 6 mg. per 100 cc. (hyperuricemia), one-third had borderline levels 5-6 mg. per 100 cc., and the rest had less than 5 mg. The coincidence of the two metabolic errors may be of interest in the study of the underlying mechanisms. The third part discusses the allergic nature of the acute gouty attack. Therapeutic trials with allergen free diets and with antihistaminic drugs are suggested.

Cholecystocolic Fistula. R. H. MARSHAK, AND W. HENKIN. Radiology, 53: 555, October, 1949.

Cholecystocolic fistula is an infrequent complication of gall-bladder disease. The pre-operative diagnosis is rarely made, and the cases are usually found incidentally during a barium enema examination. At operation the gall-bladder is generally small and buried in a mass of dense adhesions. Stones are usually present. Occasionally the fistulous tract is difficult to locate. The portions of the colon involved is invariably the hepatic flexure or the proximal transverse segment. In the 2 cases described in this article the preliminary films revealed air in the biliary system and the barium enema examination established the presence of a fistulous communication between the gall-bladder and the colon. Cholangitis did not occur in our cases nor in the cases described in the literature. Operation is not always necessary as some of the patients recorded have gone for years without difficulty. Both these patients underwent operation with an uneventful recovery.

Hypertrophic Osteoarthropathy: Report of a Case Associated with a Chordoma of the Base of the Skull and Lymphangitic Pulmonary Metastases. N. UHR, AND J. CHURG. Ann. Int. Med., 31: 681, October, 1949.

A case of rapidly fatal sphenoid-occipital chordoma is reported. The tumor destroyed the sella turcica, invaded the nasopharynx and produced diffuse lymphangitic metastases in the lungs. Even before the clinical and roentgenological evidence of pulmonary infiltration, the patient developed marked hypertrophic osteoarthropathy of the upper and lower limbs. In this connection the theory of a pituitary mechanism in hypertrophic osteoarthropathy is briefly discussed.

Emergency Psychotherapy in General Practice, Hysteria and Epilepsy. W. C. HULSE AND L. LOWINGER. Am. Prac., 4: 135, November, 1949.

Conversion hysteria represents in its simplest form the mechanism of the *conversion* of a highly distressing conflict induced anxiety into a somatic symptom-complex. The mechanism of conversion is entirely on an unconscious level, i.e., the patient is aware neither of the nature of the conflict nor of the mode of its resolution into a symptom or symptom-complex. The hysteric seizure frequently resembles in many respects an epileptic seizure: tonic and clonic movements of extremities, loss of sphincter control, and cyanosis may be present. Also, the hysteric may injure himself during a seizure. The authors indicate some differential diagnostic signs. Of all psychogenic disorders, we find in hysteria disease the purposive character of the symptoms most evident and malingering seemingly the cause. Therefore, it is essential to keep in mind that there is no element of malingering in hysteria; that the patient is not fully aware of his actions and following the attack often remembers little or nothing pertaining to his behavior during the seizure. As in hypnosis, the hysteric may carry on a conversation and when regaining his usual self, be completely unaware of all that has transpired during the seizure. During the convulsion, the hysteric is able to hear and understand everything that is said in his presence. Therefore, one must be cautious not to make any statements that may upset the patient in any way. Since communication with the patient is feasible during the seizure, the physician may commence psychotherapy by making his presence known to the patient and proceeding to state that he knows that the patient needs his help and that he is here to help him. The psychotherapeutic approach with hysteric patients is described and hysteric reactions which may pose an emergency problem to physicians are pointed out. The authors discuss in clear language the psycho-

dynamics of hysterical reactions. Since in emergencies, the least time-consuming and most effective therapeutic technique for the uncovering of the unconscious conflicts and their resolution is by means of hypnosis or narcohypnosis, the authors describe briefly the limitations and method of application of these psychotherapeutic tools. Great harm and injustice has been done to the large numbers of patients afflicted with epileptic seizures, by the widely held viewpoint that epilepsy develops on the foundation of an epileptic personality. The physician ought to realize that the epileptic patient cannot be considered as living in a vacuum, but must be considered as a person immersed in a hostile, frustrating environment who reacts to a world in which he fares so badly with deeply felt emotions of hostility, fear, guilt, and anxiety. In many epileptics such emotional factors immediately precede convulsions; in others, seizures may be induced by merely alluding to the emotionally disturbing material. The authors conclude that the mitigation of environmental problems in conjunction with analytically oriented psychotherapy may eliminate or diminish the incidence of convulsions in many epileptics. The direction which the psychotherapy is to take is briefly discussed.

The Diagnosis of Pemphigus by Its Oral Signs. L. STERN, JR. Oral Surg., Oral Med., and Oral Path., 2: 1443, November, 1949.

A series of 47 cases of pemphigus admitted to the Mount Sinai Hospital from 1926 to 1946 reveals a high incidence, 56 per cent, primary in the oral cavity. Oral involvement at some stage was noted in 83 per cent. The urgency of an early diagnosis is emphasized, with the hope that better management, or possible cure, for this disease may be developed. The differential diagnosis of the mouth lesions is therefore a point of significance. It is not unlikely that pemphigus is either a viral or bacterial disease similar to syphilis, manifesting widespread lesions of which the skin eruption may be the terminal stage. Several recent cases, of which 2 are described, were diagnosed as pemphigus well before skin lesions appeared. This diagnosis depends on the recognition of the bullae, which even in the ruptured state are distinct from ulcerative lesions. Misdiagnosis of Vincent's infection in these cases is to be guarded against, as illustrated by the 7 case abstracts in which "trench mouth" or "Vincent's infection" was the diagnosis made by the dentist or physician.

Hippuric Acid, Cinnamoylglucuronic Acid and Benzoylglucuronic Acid in the Urine of Normal Individuals and in Patients with Hepatic Dysfunction after Ingestion of Sodium Cinnamate. I. SNAPPER and A. SALTZMAN. Arch. Biochem., 24: 1, November, 1949.

A method for the quantitative estimation of cinnamic acid in urine by hydrolysis, chloroform extraction and bromine addition, is given. Normal subjects oxidize the main part of the cinnamate to benzoate and excrete it as hippuric acid. Subjects with severe liver damage oxidize cinnamate at a diminished rate; in one subject the amount of benzoate produced exceeded the capacity of the disturbed glycine mechanism with the result that some was conjugated as benzoylglucuronic acid.

A New Type of Hemolysis. B. KISCH. Exp. Med. & Surgery, 7: 377, November, 1949.

In three of thirteen investigated eels a type of hemolysis was observed not yet known in any other animal. In the red blood cells the formation of one or more prismatic shaped crystal-like bodies was observed. These bodies are growing, stretch and finally rupture their cell membrane and produce in this way the destruction and hemolysis of the red cells. All the three animals which showed this type of hemolysis were brought in by the fisherman in a deadly sick condition. It is believed that a virus infection may have been the reason.

Observations on the Hematology of Fishes and Birds. B. KISCH. Exp. Med. & Surgery, 7: 318, November, 1949.

The hemoglobin content, hematocrit and the size and amount of the red cells in the blood of different fishes and of seagulls are reported, and the size of the individual cell is approximately measured. Teleosteans have the highest red count and the smallest red

cells, selaceans the lowest count and the biggest red cells. The ganoid *Acipenser* behaves, with reference to the blood count, hemoglobin and hematocrit, like a selacean, and in respect to the urea content of the blood, like a teleostean. The investigated sharks have approximately the same hemoglobin content as *Raja Eglanteria* and *Raja Stab.*, but their blood count is higher and the size of the red cells smaller than in the rays.

Electrocardiographic Studies in Seagulls. B. KISCH. *Exp. Med. & Surgery*, 7: 345, November, 1949.

The hearts of five seagulls were investigated with standard leads, chest leads and with semi-unipolar direct leads (Wilson's Central Terminal). The rate in light ether narcosis was in the average 447 (Maximum 500, minimum 410). The auricular complex does not differ significantly from that of all other vertebrates investigated up to now. The average P-R interval is 0.05, the average R-T interval 0.12 sec. The significant features of the ventricular electrogram of the seagull are described in detail, also their differing from the human electrogram. Nearest to the human type is that of the rabbit and dog, and nearest to the bird (seagull) type is that of the calf. The slowing of the heart rate can be produced by cooling the venoauricular junction, by dyspnea and by acetylcholine. Local application of acetylcholine on the right auricle evokes auricular flutter and fibrillation. This may be done repeatedly on the same heart. The similarity between right wing potentials and cavity potentials in birds seems to prove the influence of the cavity potential on the right extremity potentials, and strongly supports a similar conclusion in man and other vertebrates.

Lead Poisoning Diagnosed by the Presence of Nuclear Acid-fast Inclusion Bodies in Kidney and Liver. M. WACHSTEIN. *Arch. Path.*, 48: 442, November, 1949.

The cause of death in a 21 month old boy was clarified by the findings of nuclear inclusion bodies in the liver and kidneys. On the basis of their morphologic aspect and acid-fastness the inclusions were assumed to be caused by lead. Chemical examination of kidney and liver tissue confirmed this assumption. Nuclear inclusion bodies are of considerable significance for the diagnosis of lead poisoning in tissues.

Hepatosplenomegaly and Liver Damage in Graves Disease. R. S. WALLERSTEIN, AND W. J. WALKER. *Ann. Int. Med.*, 31: 904, November, 1949.

A case of relatively mild thyrotoxicosis with concomitant marked liver damage and secondary hepatosplenomegaly is presented. The literature concerning the clinical, biochemical, pathological, and experimental evidence of the presence of impaired hepatic function as an integral part of the syndrome of thyrotoxicosis is reviewed. Attention is called to the fact that the liver damage can be severe enough to cause definite enlargement of the liver and spleen and that these findings though unusual are completely compatible with the clinical picture of thyrotoxicosis. In this patient, the hepatic dysfunction was reversed after subtotal thyroidectomy.

Carcinoma of the Colon and Rectum. A Ten Year Study. J. H. GARLOCK AND S. H. KLEIN. *Arch. Surg.*, 59: 1289, December, 1949.

A series of 910 cases of cancer of the colon and rectum is presented and analyzed in groups subdivided according to the anatomical location of the lesion namely, ascending colon, transverse colon, sigmoid and descending colon, and the rectosigmoid and rectum. The entire series consists of 2 comparable groups composed of 549 ward patients and 361 private patients. The operability and operative mortality rates are analyzed and the reasons for the more favorable results obtained in the private group as compared with those in the ward service are discussed. The data presented in the paper indicate that the operation of obstructive resection is still an excellent one and should not be discarded in the present wave of enthusiasm for the operation of resection and primary anastomosis. The surgical conditions under which the latter procedure seems to be contraindicated are outlined.

Follow-up studies indicate that the greatest number of long term survivors are to be found in the group without metastatic lymph node involvement at the time of operation.

Isolation of Hyaluronic Acid from the Cock's Comb. N. F. BOAS. J. Biol. Chem., 181: 573, December 1949.

Hyaluronic acid is present in the cock's comb in appreciable quantity. Aqueous extraction methods were used and its identification was based upon its viscosity, its reaction with hyaluronidase, its glucosamine, nitrogen and acetyl content, and on its electrophoretic pattern. This explains the metachromasia in the cock's comb observed with the use of certain basic dyes, such as toluidine blue and thionine.

Observations on the Extinction Phenomenon in Hemiplegia. M. B. BENDER, M. F. SHAPIRO AND A. M. SCHAPPELL. Arch. Neurol. & Psychiat., 62: 717, December, 1949.

In a study of the cutaneous sensory responses of 50 hemiplegics it was determined that double simultaneous stimulation revealed sensory deficits not ordinarily demonstrable by the usual methods of examination and that the most effective D.S.S. technique was the simultaneous stimulation of nonhomologous regions of the 2 sides of the body. A pattern of sensory dominance on the hemiplegic side in the descending order of face, thigh, shoulder, foot and hand was demonstrable. A previously unreported phenomenon of patterned sensory mislocalizations on the affected side was described. It was further shown that adequate sensory examinations can be performed on aphasic and psychotic patients.

Aerosols I. The Urinary Excretion of Inhaled Phenolsulfonphthalein Mists. H. A. ABRAMSON, C. REITER, H. H. GETTNER, AND B. SKLAROFESKY. Ann. Allergy, 7: 761, November/December, 1949.

By means of phenolsulfonphthalein aerosols data have been obtained on the absorption of phenolsulfonphthalein from the lungs following inhalation of aerosols of this dye. The experiments were mainly carried out using the nasal route so that inhalation occurred in a closed system. The effect of baffling by the nose and upper respiratory tract as well as swallowing of the dye is shown to be of minor importance with the main quantity of the dye appearing in the urine dependent upon absorption through the mucous membrane of the lungs. The following variables have been studied and data pertinent thereto: (1) effect of the initial concentration of the dye in the nebulizer on urinary excretion of the dye, (2) the effect of increasing the volume of the dye, (3) the effect of shrinkage of the nasal mucosa, (4) absorption from the nasal mucosa and excretion in the urine, (5) the effect of glycerine to increase deposition and absorption of the dye in the lungs, (6) the reproducibility of renal excretion of the dye, (7) the ratio of the dye excreted in the urine to the dye delivered by the nebulizer to the patient. It is concluded from the experiments that a larger number of variables are in our present technique of antibiotic therapy than are desirable. The delivery of the nebulizer should be studied with a view to standardizing lung absorption and lung permeability. The inspiration time rather than the total time of administration was concluded to be of importance. An inspiration-time meter was devised and will be described in a following communication.

Rectosigmoidal Electrode. R. TURELL. West. J. Surg., 57: 596, December, 1949.

The author described in detail and illustrated ball-tipped electrodes suitable for desiccation of new growths in the rectum and rectosigmoid.

Investigation of Contact-Type Dermatitis Due to Compound Tincture of Benzoin. K. STEINER AND W. LEIFER. J. Invest. Derm., 13: 351, December, 1949.

Studies were made on 3 patients who developed sensitivity to compound tincture of benzoin used as a skin protective before application of adhesive tape. Patch tests were made on 2 patients with the major components (benzoin, tolu, storax, and aloes) and all gave positive reactions. On the same 2 patients patch tests were made with some impor-

tant ingredients of these plant derivatives: benzoid acid was positive in 1 patient in whom cinnamic acid and vanillin were negative; in the second patient cinnamic acid was positive, while benzoic acid and vanillin were negative. It was conjectured that some common unidentified substance, perhaps a terpene, was responsible for the reactions, or that chemical changes in the skin resulted in a common sensitizing breakdown product.

Simple Lymphoma of the Sphincteric Rectum in Identical Twins. E. GRANET. J. A. M. A., 141: 990, December, 1949.

Two cases of simple lymphoma of the sphincteric rectum occurring in identical twins are recorded. It is probable that lymphomas of the anorectum occur more commonly than is evident from cases reported in the literature. It must again be emphasized (as has been repeatedly pointed out by Hellwig, Rosser, Tom Smith, Buie and others) that purportedly benign lesions of the anorectum may be potentially or actually cancerous. Of the 54 cases of lymphomas of the sphincteric rectum and anus reported in the last 2 decades, 26 were malignant lymphomas or lymphosarcomas. Clinically the correct diagnosis of these lesions is impossible, as they too often resemble one of the numerous types of benign lesions so commonly found in this site. It becomes mandatory, therefore, that surgeons submit tissue from all lesions excised from the anorectum for careful microscopic examination by competent pathologists.

The Master "Two-Step" Exercise Test in the Differential Diagnosis of Coronary Artery Disease. S. STORCH, L. PORDY, AND J. KOLKER. New York State J. Med., 49: 2843, December, 1949.

The case of a man 60 years of age with a history of severe gastrointestinal bleeding on 3 previous occasions who was admitted to the Mount Sinai Hospital because he began to experience sudden attacks of syncope is described. The physical examination, laboratory examination of blood, urine, and feces and resting electrocardiogram were normal. There was no evidence of bleeding, and the neurological examination was negative. The patient was referred to the cardiographic department for study. A standard "2-step" exercise test showed marked RS-T segment depressions in leads I, II, V₄ in the tracing taken immediately following exercise, and a diagnosis of coronary artery disease with severe coronary insufficiency was made. A standard 10 per cent anoxemia test was also performed and confirmed this diagnosis by the presence of conspicuous depressions of the RS-T segment in leads I, II and V₄. This diagnosis was corroborated further when 9 months later the patient suffered an acute coronary occlusion with infarction involving the posterior wall of the left ventricle.

Diagnosis and Treatment of Acute Coronary Diseases. A. M. MASTER, S. DACK, L. E. FIELD, AND H. HORN. J. A. M. A., 141: 887, November, 1949.

Acute Coronary Occlusion is a prolonged illness, which may leave its earmarks for years. In acute coronary insufficiency the prognosis is variable but better as a whole; it depends on the precipitating factor. It is only occasionally fatal. The duration of the illness is minutes, days or weeks. The condition after an attack is variable. Acute coronary insufficiency, like acute coronary occlusion, is a complete entity with its own definite predisposing and precipitating factors, with its peculiar pathology and physiology, with a characteristic electrocardiogram and, most important of all, with a preventive, prophylactic and curative treatment.

Prognosis After Nephrectomy for Renal Tuberculosis. G. D. OPPENHEIMER AND L. NARINS. J. Urol., 62: 804, December, 1949.

A study of 106 patients who had unilateral nephrectomy for renal tuberculosis from 1928 through 1945 is presented. On the basis of careful follow-up records, survival rates and developments were determined. It was concluded that nephrectomy for unilateral renal tuberculosis offers a better than even chance for a 5-10 year cure and proves that this

method of treatment is reliable. These patients were treated without the benefits of streptomycin or other antibiotics.

Embolization with Material from Atheromata. F. G. ZAK AND K. ELIAS. *Am. J. M. Sc.*, 218: 510, November, 1949.

Although mentioned in some of the older textbooks, the occurrence of embolization with atheroma material has fallen into oblivion. The histologic picture of this process has only recently been established. Most of the cases seen by pathologists represent the late or healed phase. It is shown that the acute phase impresses as a panarteritis which may necessitate serial sections for elucidation; foreign body giant cell reaction and intimal thickening are later phases. The embolic material does not necessarily come from aortic atheroma but may occasionally arise in a systemic artery or an atheromatous valve ring. Embolization with atheroma material is not too rare. It is possible that a good number of cases with transient or permanent impairment of peripheral, visceral or cerebral circulation can thus be accounted. Pathologists and neuropathologists should prove its presence in any given case.

Design of a Pump Suitable for Blood. A. SALTZMAN AND S. S. ROSENAK. *J. Lab. & Clin. Med.*, 34: 1561, November, 1949.

A pump is described that conveys blood under sterile precautions with a minimal degree of hemolysis. It contains a Tygon tube which is compressed in a wave-like motion by a series of 12 keys that push the column of fluid ahead. No shearing motion is possible since the keys can move only in the vertical plane.

Current Concepts of Hemolytic Anemias. SOLOMON ESTREN AND WILLIAM DAMESHEK. *Advances in Internal Medicine*, 3: 45, 1949.

This article is a comprehensive review of our knowledge of the problems of the hemolytic anemias. The authors discuss first basic questions concerning the formation and destruction of the red blood cell, including the life-span of the red cell, the metabolism of hemoglobin, the fate of the hemoglobin pigments, the sites and manner of red cell destruction, and the role of the reticulo-endothelial system, including the spleen. The various hemolytic anemias are then classified into two large groups: those in which the fundamental abnormality is in the red cell; and those in which the red cell itself is fundamentally normal, but the mechanism for hemolysis lies elsewhere. Each hemolytic process in each of these categories is considered in detail. There is a section on immunohematology as related to hemolysis (antibodies), a note on "siderocytic" anemias, and a discussion of "hypersplenic" hemolytic anemias.

Pulmonary Embolism: Its Incidence at Necropsy in Relation to Peripheral Thrombosis. N. ROSENTHAL, J. M. WEINER, S. SHAPIRO. *Ann. Int. Med.*, 31: 884, November, 1949.

The necropsy protocols of a large series of cases in a chronic disease hospital were carefully analysed to test the truth of the common presumption that the incidence of pulmonary embolism parallels that of thrombosis in any given age or disease group. The incidence of significant thrombosis in the age groups above fifty was twice that below fifty. The incidence of pulmonary embolism however, did not manifest a major increase until the seventh decade. In ninety-seven cases of portal cirrhosis, despite the fact that this group did not differ significantly in the amount of cardiac and peripheral venous thrombosis from the miscellaneous group, there were no pulmonary emboli. This contrasts with the 10% to 20% of pulmonary emboli in the other disease groups. There is a definite dissociation of the incidence of pulmonary embolism and peripheral thrombosis. In Laennec cirrhosis there is a negligible incidence of pulmonary embolism, but not of peripheral thrombosis for reasons not understood.

Structure of 1,2,3,4,5,6-Hexasubstituted Cyclohexanes. H. SOBOTKA. Research, 2: 393, November, 1949.

This paper deals with the cis-trans isomerisms of hexa-substituted cyclohexanes and the possibility of a new type of isomerism.

The Partial Reduction of an Enzyme System by Lithium Aluminum Hydride. J. D. CHANLEY AND H. SOBOTKA. J. Am. Chem. Soc., 71: 4140, December, 1949.

This describes the first instance of the partial hydrogenation of a triple bond to a double bond by lithium aluminum hydride. The resulting trisnor- β -ionol was subsequently oxidized to trisnor- β -ionone. Discussion of the absorption spectra in the vitamin A group is included.

Synthesis of 1-Dehydro- β -Ionone. H. SOBOTKA AND J. D. CHANLEY. J. Am. Chem. Soc., 71: 4136, December, 1949.

The preparation of many intermediates in the synthesis of vitamin A is described; the acetylenic analogs of β -ionone and β -ionol were prepared and their structure confirmed.

ERRATUM

The March-April issue of this Journal (Volume XVIII, Number 6, page 371) carries a brief abstract on "Colonic and Proctologic Diseases" by R. Turell and A. S. Lyons. A correction is to be made as to the Journal in which it appears. It should read: Internat. Abstr. Surg., 89: 105, 1949; in Surg., Gynec. & Obst., August, 1949.

INDEX TO NUMBER 1, VOLUME NINETEEN

The (*) preceding the page number indicates an original article; the letters "ab" similarly placed indicate an abstract. Author entries are made only for original articles.

- A**CTH, cortisone, and prolactin, effect of excessive doses of, in pregnant and nursing mice, *84
- Action of fluoride on the heart of rana pipiens, preliminary note, *1
- Acute gastric dilatation, *310
- Adenoma of the bronchus, endoscopic treatment in selected cases, (M. L. Som), ab360
- Adlersberg, David, Coronary atherosclerosis in the young: clinical and pathologic observations, *289
- Adrenal cortex, Cushing's syndrome due to tumor of, (H. M. Goldstein), ab359
- Aerosol delivery and stability during nebulization, procedure for determination of, (H. A. Abramson, et al.), ab362
- I, the urinary excretion of inhaled phenosulfonphthalein mists, (H. A. Abramson), ab371
- Aged, indications of bed rest, particularly in the, *131
- Alarm reaction, the relationship of chronic recurrent sialadenitis to the, (H. E. Bass and M. Mendlowitz), ab364
- Albrecht, M., see Heubner, W., *47
- Allergy, physiologic and pathologic, *240
- Amino acids on the nephrotoxic action of dl-ethionine, the influence of experimental hydronephrosis and of several, *221
- Amyloidosis in multiple myeloma, progress noted in 50 years of personal observation, *8
- Analgetika, über Angriffspunkt und Wirkungsweise Morphinähnlich Wirkender, *154
- Anemia, sickle cell, collapse of the vertebral bodies in, (W. A. Henkin), ab363
- Anemias, current concepts of hemolytic, (Solomon Estren and William Dameshek), ab373
- Angriffspunkt und Wirkungsweise Morphinähnlich wirkender Analgetika, *154
- Antiaccelerator cardiac agents, *53
- Antibiotics: penicillin and streptomycin, the mode of action of, *175
- Antopol, William, The changing pattern of infectious processes under the influence of cortisone, *91
- Appendicopathie, ueber die Neurogene, *30
- Arnold, Ottokar, Die Bedeutung der Experimentellen Pharmakologie fur die Neurologie und Psychiatrie, *191
- Arteriosclerosis, human and experimental, *106
- Atherosclerosis, coronary, in the young: clinical and pathologic observations, *289
- Arzt, L., Disseminated lupus erythematosus, (malignant lupus erythematosus (Goldsmith-Bear)). Seine Geschichte—Versuch einer Begriffsbestimmung, *19
- Automatik und deren Grenzen, *38
- B**AEHR, George, Tribute to a lost world, *xiv
- Barocke, E., see Heubner, W., *47
- Bed rest, indications of, particularly in the aged, *31
- Bedeutung der experimentellen Pharmakologie für die Neurologie und Psychiatrie, *191
- Benzolglucuronic acid, hippuric acid, cinnamoylglucuronic acid, in the urine of normal individuals and in patients with hepatic dysfunction after ingestion of sodium cinamate, (I. Snapper and A. Saltzman), ab369
- Bile canaliculi, intracellular, in the rabbit liver. (17391), (M. Wachstein), ab366
- Blood pressures of chronic hypertensive dogs surviving bilateral nephrectomy, *266
- Bronchialmuskelkrampf, die Wirkung elektrischer Hypothalamusreizung auf den experimentell erzeugten, *10
- Brücke, F. v., Die elektrischer Hypothalamusreizung auf den experimentell erzeugten bronchial Muskelkrampf, *10
- Bundle branch block, modifications of the heart sounds in, *70
- C**ARCINOMA in chronic ulcerative colitis, on the incidence of, *275
- of the colon and rectum, a ten year study, (J. H. Garlock and S. H. Klein), ab370
- Cardiac agents, antiaccelerator, *53
- Carotene in man, studies on serum, (D. Adlersberg, et al.), ab364
- Cataract suture, a simple and efficient, (J. Laval), ab360
- Catecholamines, mineralocorticoids and sodium in hyper- and hypotension, the integrated role of, *233
- Cerletti, A., see Rothlin, E., *138
- Changing pattern of infectious processes under the influence of cortisone, *91
- Chiari, H., Ueber die Neurogene Appendicopathie, 30
- Cholecystocolic fistula, (R. H. Marshak and W. Henkin), ab368
- Chorda tympani nerve graft, (Samuel Rosen), ab364
- Churg, Jacob, see Lehr, David, *106
- Circulation, renal, experimental studies on, *138

- Colitis, ulcerative, on the incidence of carcinoma in chronic, *275
- Colon and rectum, carcinoma of the, a ten year study, (J. H. Garlock and S. H. Klein), ^{ab}370
- Complement, fixation of, with the purified factor in mouse milk connected with mammary carcinoma, *210
- Contro, Stephen, Modifications of the heart sounds in the bundle branch block, *70
- Convulsions in relation to age, susceptibility to, *4
- Coronary artery disease, the Master "two-step" exercise test in the differential diagnosis of, (S. Storch, et al.), ^{ab}372
- Coronary atherosclerosis in the young: clinical and pathologic observations, *289
- diseases, diagnosis and treatment of acute, (A. M. Master, et al.), ^{ab}372
- insufficiency, acute, due to pulmonary embolism, (S. Dack, et al.), ^{ab}367
- thrombosis, traumatic, with myocardial infarction, (H. Levy), ^{ab}360
- Cortisone, ACTH, and prolactin, effect of excessive doses of, in pregnant and nursing mice, *84
- the changing pattern of infectious processes under the influence of, *91
- Cushing's syndrome due to tumor of adrenal cortex, (H. M. Goldstein), ^{ab}359
- D**E LA HUERGA, Jesus, see Popper, Hans, *256
- Dermatitis, contact-type, due to compound tincture of benzoin, investigation of, (K. Steiner and W. Leifer), ^{ab}371
- contact allergic, due to the procaine fraction of procaine penicillin, (S. M. Peck and F. F. Feldman), ^{ab}364
- Desoxycorticosterons und anderer Sterine auf die Zellmembrandurchlässigkeit der Gelenkkapsel, Einfluss des, *185
- Diabetes mellitus, problems in juvenile, *249
- Diagnosis of hyperthyroidism, laboratory aids in the, *345
- Dibenamine, the use of, in pheochromocytoma and detection of pressor activity of the plasma by bio-assay, *320
- Dieumarol in congestive heart failure, the increased hypoprothrombinemic effect of a small dose of, (D. Stats), ^{ab}363
- Disseminated lupus erythematosus, (malignant lupus erythematosus (Goldsmith-Bear)). Seine Geschichte—Versuch einer Begriffsbestimmung, *19
- Dl-ethionine, the influence of experimental hydronephrosis and of several amino acids on the nephrotoxic action of, 221
- Drug action, progress in our pharmacological knowledge of, (E. P. Pick), ^{ab}361
- Drugs into the milk, the transfer of, *210
- Durig, A., Über Automatik und Deren Grenzen, *38
- E**CCRINOLOGICAL classification of gastric mucus, *328
- Effect of excessive doses of cortisone, ACTH and prolactin in pregnant and nursing mice, *84
- of histamine on the isolated sympathetic ganglion, *149
- of some reagents on the fluorescence of stilbamidine and 2 OH-Hydroxystilbamidine in vitro, *217
- of thiourea on mitosis in rat livers damaged by carbon tetrachloride, *339
- Einfluss des Desoxycorticosterons und anderer Sterine auf die Zellmembrandurchlässigkeit der Gelenkkapsel, *185
- Electrocardiographic studies in seagulls, (B. Kisch), ^{ab}370
- Electrode, rectosigmoidal, (R. Turell), ^{ab}371
- Elektrokymography, some clinical applications of, findings in myocardial infarction and heart block, (M. L. Sussman, et al.), ^{ab}366
- Electrosurgical snare, sigmoidorectal, (R. Turell), ^{ab}365
- Elektrischer Hypothalamusreizung, die Wirkung, auf den experimentell erzeugten Bronchiamuskelkrampf, *10
- Embolism, pulmonary, acute coronary insufficiency due to, (S. Dack, et al.), ^{ab}367
- pulmonary, its incidence at necropsy in relation to peripheral thrombosis, (N. Rosenthal, et al.), ^{ab}373
- Embolization with material from atheromata, (F. G. Zak and K. Elias), ^{ab}373
- Encephalopathy following pertussis vaccine prophylaxis, (J. H. Globus and J. L. Kohn), ^{ab}367
- Enzymes, hepatic, and serum, in experimental liver damage, *256
- Ernest Peter Pick, the scientist, *xii
- Eugenol, histological study of the destruction and regeneration of the gastric mucous barrier following application of, preliminary report, (F. Hollander and R. Goldfischer), ^{ab}365
- Experimental hydronephrosis, the influence of, and of several amino acids on the nephrotoxic action of dl-ethionine, *221
- studies on renal circulation, *138
- Experimentellen Pharmakologie für die Neurologie und Psychiatrie, die Bedeutung der, *191
- Extinction phenomenon in hemiplegia, observations on the, (M. B. Bender, et al.), ^{ab}371
- F**EITELBERG, Sergei, see Silver, Solomon, *345
- Female genital organs, the influence of toxic agents on the, a brief review, *333
- Fibroblastenkulturen, Gewöhnungsversuche an, *47
- Finkelstein, William E., see Zak, Frederick G., *352
- Fistula, cholecystocolic, (R. H. Marshak and W. Henkin), ^{ab}368
- Fixation of complement with the purified

- factor in mouse milk connected with mammary carcinoma, *210
- Fleischmann, Susan Kann, see Fleischmann, Walter, *228
- Fleischmann, Walter, Uptake of P^{32} in seminal vesicles of castrate rats after treatment with testosterone propionate, *228
- Fluorescence of stilbamidine and 2 OH-hydroxystilbamidine in vitro, *217
- Fluoride on the heart of rana pipiens, on the action of, preliminary note, *1
- Foreword, *ix
- Freud, Paul, The relationship of xanthoma juvenile to systemic reticuloendotheliosis, *243
- Friedberg, Charles K., Problems in the management of refractory heart failure, *303
- Froehlich, Alfred, Susceptibility to convulsions in relation to age, *4
- G**ASTRIC dilatation, acute, *310
- mucous barrier following application of eugenol, histological study of the destruction and regeneration of the, preliminary report, (F. Hollander and R. Goldfischer), ^{ab}365
- mucosa, prolapsed, a possible cause of "gastric" symptoms in right heart failure, (M. Melamed and A. Melamed), ^{ab}359
- mucus, the eccrinological classification of, *328
- Gelenkkapsel, Einfluss des Desoxycorticosterons und anderer Sterine auf die Zellmembrandurchlässigkeit der, *185
- Gewöhnungsversuche an Fibroblastenkulturen, *47
- Glaubach, Susi, Effect of excessive doses of cortisone, ACTH and prolactin in pregnant and nursing mice, *84
- Glaucoma, advanced chronic simple, therapeutic results in, with telescopic fields, (S. Bloomfield and L. Kellerman), ^{ab}363
- Globus, Joseph H., Foreword, *ix
- Gold, Ernest, Acute gastric dilatation, *310
- Gout, newer advances in, (D. Adlersberg), ^{ab}367
- Graff, Samuel, see Heidelberger, Michael, *210
- Some observations on nucleic acids, *313
- Grafting with lymphosarcoma cells, resistance to, in rats injected with homologous lymphoid cells, *169
- Graves disease, hepatosplenomegaly and liver damage in, (R. S. Wallerstein and W. J. Walker), ^{ab}370
- Gustus, Ida L., see Fleischmann, Walter, *228
- H**AAGENSEN, C. D., see Heidelberger, Michael, *210
- Haimovici, Henry, The use of dibenamine in pheochromocytoma and detection of pressor activity of the plasma by bioassay, *320
- Hair-Waving process, the cold permanent, (H. T. Behrman, et al.), ^{ab} 360
- Halpern, Mark, see Friedberg, Charles K., *303
- Häusler, Hans F., Zur Frage der Übertragung Sensibler Impulse im Rückenmark des Frosches, *121
- Heart block, the findings in myocardial infarction and, some clinical applications of electrokymography, (M. L. Sussman, et al.), ^{ab}366
- disease, arteriosclerotic, vitamin E in, with electrocardiographic evidence, (M. E. Eisen and H. Gross), ^{ab}366
- failure, refractory, problems in the management of, *303
- failure, right, prolapsed gastric mucosa, a possible cause of "gastric" symptoms in, (M. Melamed and A. Melamed), ^{ab}359
- failure, the increased hypoprothrombinemic effect of a small dose of dicumarol in congestive, (D. Stats), ^{ab}363
- of rana pipiens, on the action of fluoride on the, preliminary note, *1
- sounds, modifications of the, in bundle branch block, *70
- Heidelberger, Michael, Fixation of complement with the purified factor in mouse milk connected with mammary carcinoma, *210
- Hematology of fishes and birds, observations on the, (B. Kisch), ^{ab}369
- Hemolysis, a new type of, (B. Kisch), ^{ab}369
- Hepatic and serum enzymes in experimental liver damage, *256
- Hepatosplenomegaly and liver damage in Graves disease, (R. S. Wallerstein and W. J. Walker), ^{ab}370
- Heubner, W., Gewöhnungsversuche an Fibroblastenkulturen, *47
- Hippuric acid, cinnamoylglucuronic acid and benzoylglucuronic acid in the urine of normal individuals and in patients with hepatic dysfunction after ingestion of sodium cinnamate, (I. Snapper and A. Saltzman), ^{ab}369
- Histamine effect of, on an isolated sympathetic ganglion, *149
- Hoff, Hans, see Arnold, Ottokar, *191
- Hollander, Franklin, The eccrinological classification of gastric mucus, *328
- Human and experimental arteriosclerosis, *106
- Hyaluronic acid from the cock's comb, isolation of, (N. F. Boas), ^{ab}371
- Hydronephrosis, the influence of experimental, and of several amino acids on the nephrotoxic action of dl-ethionine, *221
- Hypertensive dogs, chronic, surviving bilateral nephrectomy, blood pressures of, *266
- Hyperthyroidism, laboratory aids in the diagnosis of, *345

Hypothalamusreizung, die Wirkung elektrischer, auf den experimentell erzeugten Bronchialmuskelskrampf, *10

INCIDENCE of carcinoma in chronic ulcerative colitis, *275

Indications of bed rest, particularly in the aged, *131

Infectious processes under the influence of cortisone, the changing pattern of, *91

Influence of experimental hydronephrosis and of several amino acids on the nephrotoxic action of dl-ethionine, *221 of toxic agents on the female genital organs, a brief review, *333

Integrated role of catecholamines, mineralocorticoids and sodium in hyper- and hypotension, *233

Isotopically labeled nirvanol, *212

KAINDEL, F., see Brücke, F. v., *10

Kewitz, H., see Heubner, W., *47

Koch-Weser, Dieter, see Popper, Hans, *256

Konzett, H., The effect of histamine on an isolated sympathetic ganglion, *149

Krayer, Otto, Antiaccelerator cardiac agents, *53

LABORATORY aids in the diagnosis of hyperthyroidism, *345

Lead poisoning diagnosed by the presence of nuclear acid-fast inclusion bodies in kidney and liver, (M. Wachstein), ^{ab}370

Legg-Perthes' disease, roentgen examination of the hip in, (S. Siffert and E. H. Bettman), ^{ab}366

Lehr, David, Human and experimental arteriosclerosis, *106

Leon, Myron A., see Heidelberger, Michael, *210

Lieben, F., Effect of some reagents on the fluorescence of stilbamidine and 2 OH-hydroxystilbamidine in vitro, *217

Liver biopsy, guided, through laparotomy incision, (E. E. Jemerin), ^{ab}366 damage in Graves disease, hepatosplenomegaly, (R. S. Wallerstein and W. J. Walker), ^{ab}370

damage, serum and hepatic enzymes in experimental, *256

Livers, rat, damaged by carbon tetrachloride, the effect of thiourea on mitosis in, *339

Loewe, S., "Nicotinic Activity" and the problem of pharmacologic selectivity, *160

Loewi, O., On the action of fluoride on the heart of rana pipiens, preliminary report, *1

Ernest Peter Pick, the scientist, *xii

Luisada, Aldo A., see Contro, Stephen, *70

Lupus erythematosus, disseminated, (malignant lupus erythematosus (Goldsmith-Bear)). Seine Geschichte—Versuch einer Begriffsbestimmung, *19

Lymphoma, simple, of the sphincteric rectum in identical twins, (E. Granet), ^{ab}372

Lymphosarcoma cells, resistance to grafting with, in rats injected with homologous lymphoid cells, *169

MAGNUS-LEVY, A., Amyloidosis in multiple myeloma, progress noted in 50 years of personal observation, *8

Master "two-step" exercise test in the differential diagnosis of coronary artery disease, (S. Storch, et al.), ^{ab}372

Mautner, Hans, the transfer of drugs into the milk, *83

Mayer, H., see Brücke, F. v., *10

Meisel, E., see Wachstein, M., *221

Milk, mouse, fixation of complement with the purified factor in, connected with mammary, *210

Milk, the transfer of drugs into the, *83

Mineralocorticoids, catecholamines, and sodium in hyper- and hypotension, the integrated role of, *233

Mitosis in rat livers damaged by carbon tetrachloride, the effect of thiourea on, *339

Mode of action of antibiotics: penicillin and streptomycin, *175

Modifications of the heart sounds in bundle branch block, *70

Morphinähnlich Wirkender Analgetika, über Angriffspunkt und Wirkungsweise, *154

Mueller-Deham, Albert, Indications of bed rest, particularly in the aged, *131

Myeloma, amyloidosis in multiple, progress noted in 50 years of personal observation, *8

NEBULIZATION, procedure for determination of aerosol delivery and stability during, (H. A. Abramson, et al.), ^{ab}362

Nephrectomy, bilateral, blood pressures of chronic hypertensive dogs surviving, *266

for renal tuberculosis, prognosis after, (G. D. Oppenheimer and L. Narins), ^{ab}372

Neumayr, A., see Brücke, F. v., *10

Neurogene Appendicopathie, Ueber die, *30

"Nicotinic activity" and the problem of pharmacologic selectivity, *160

Nirvanol, isotopically labeled, *212

Novak, Josef, The influence of toxic agents on the female genital organs, a brief review, *333

Nucleic acids, some observations on the, *313

OGINSKY, E. L., see Umbreit, W. W., *175

Oppenheimer, B. S., Blood pressures of chronic hypertensive dogs surviving bilateral nephrectomy, *266

Oppenheimer, Gordon D., see Oppenheimer, B. S., *266

Osteoarthropathy, hypertrophic, report of a case associated with a chordoma of the skull and lymphangitic pulmonary metastases, (N. Uhr and J. Churg), ^{ab368}

Otani, Sadao, On the incidence of carcinoma in chronic ulcerative colitis, *275

PARTIAL reduction of an enzyme system by lithium aluminum hydride, (J. D. Chanley and H. Sobotka), ^{ab374}

P³², uptake of, in seminal vesicles of castrate rats after treatment with testosterone propionate, *228

Pemphigus, the diagnosis of by its oral signs, (L. Stern, Jr.), ^{ab369}

Penicillin, procaine, contact allergic dermatitis due to the procaine fraction of, (S. M. Peck and F. F. Feldman), ^{ab364} and streptomycin, the mode of action of antibiotics, *175

Pertussis vaccine prophylaxis, encephalopathy following, (J. H. Globus, and J. L. Kohn), ^{ab367}

Pharmacologic selectivity, "nicotinic activity" and the problem of, *160

Pharmakologie für die Neurologie und Psychiatrie, die Bedeutung der experimentellen, *191

Pheochromocytoma, the use of dibenamine in, and detection of pressor activity of the plasma by bio-assay, *320

Physiologic and pathologic allergy, *240

Pick, Ernest Peter, the scientist, *xii

Pituitary adenoma, roentgen therapy for, (A. L. Bachman and W. Harris), ^{ab362}

Plumbism in children, *352

Popper, Hans, Serum and hepatic enzymes in experimental liver damage, *256

Problems in juvenile diabetes mellitus, *249 in the management of refractory heart failure, *303

Prolactin in pregnant and nursing mice, effect of excessive doses of cortisone, ACTH and, *84

Psychiatric observations concerning rhinoplasty, (L. Linn and I. B. Goldman), ^{ab365}

Psychotherapy, emergency, in general practice, hysteria and epilepsy, (W. C. Hulse and L. Lowinger), ^{ab368}

Pump suitable for blood, design of a, (A. Saltzman and S. S. Rosenak), ^{ab373}

QUITTNER, Howard, see Antopol, William, *91

RAAB, W., The integrated role of catecholamines, mineralocorticoids and sodium in hyper- and hypotension, *233

Rachmilewitz, M., The effect of thiourea on mitosis in rat livers damaged by carbon tetrachloride, *339

Raper, Ruth S., see Fleischmann, Walter, *228

Reagents, effect of some, on the fluorescence

of stilbamidine and 2 OH-hydroxy-stilbamidine in vitro, *217

Rectosigmoidal electrode, (R. Turell), ^{ab371}

Rectum, carcinoma of the colon and, a ten year study, (J. H. Garlock and S. H. Klein), ^{ab370}

simple lymphoma of the sphincter, in identical twins, (E. Granet), ^{ab372}

Relationship of xanthoma juvenile to systemic reticuloendotheliosis, *243

Renal circulation, experimental studies on, *138

Resistance to grafting with lymphosarcoma cells in rats injected with homologous lymphoid cells, *169

Reticuloendotheliosis, the relationship of xanthoma juvenile to systemic, *243

Rhinoplasty, psychiatric observations concerning, (L. Linn and I. B. Goldman), ^{ab365}

Roentgen therapy for pituitary adenoma, (A. L. Bachman and W. Harris), ^{ab362}

Rosenak, Stephen S., see Oppenheimer, B. S., *266

Rosin, A., see Rachmilewitz, M., *339

Rothlin, E., Experimental studies on renal circulation, *138

Rückenmark des Frosches, zur Frage der Übertragung sensibler Impulse im, *121

SCHLAUMANN, O., Über Angriffspunkt und Wirkungsweise Morphinähnlich wirkender Analgetika, *154

Schick, Bela, Physiologic and pathologic allergy, *240

Schistosoma mansoni, longevity of, observations based on a case, (R. S. Wallerstein), ^{ab363}

Selectivity, pharmacologic, "nicotinic activity" and the problem of, *160

Seminal vesicles of castrate rats after treatment with testosterone propionate, uptake of P³², *228

Sensibler Impulse im Rückenmark des Frosches, zur Frage der Übertragung, *121

Serum and hepatic enzymes in experimental liver damage, *256

carotene in man, studies on, (D. Adlersberg, et al.), ^{ab364}

Sialadenitis, the relationship of chronic recurrent, to the alarm reaction, (H. E. Bass and M. Mendlowitz), ^{ab364}

Sigmoidorectal electrosurgical snare, (R. Turell), ^{ab365}

Silver, Solomon, Laboratory aids in the diagnosis of hyperthyroidism, *345

Snapper, Isidore, see Otani, Sadao, *275

Sobotka, Harry, Isotopically labeled nirvanol, *212

Sodium in hyper- and hypotension, the integrated role of catecholamines, mineralocorticoids and, *233

Sterine auf die Zellmembrandurchlässigkeit der Gelenkkapsel, Einfluss des Desoxycorticosterons und anderer, *185

- Stern, P., Einfluss des Desoxycorticosterons und anderer Sterine auf die Zellmembrandurchlässigkeit der Gelenkkapsel, *185
- Sterz, Heinz, see Häusler, Hans F., *121
- Stillbamidine and 2 OH-hydroxystilbamidine in vitro, effect of some reagents on the fluorescence of, *217
- Streptomycin in the treatment of whooping cough, (Lewis Wanamaker, et al.), ^{ab}359
- penicillin, the mode of action of antibiotics, *175
- Structure of 1,2,3,4,5,6-hexasubstituted cyclohexanes, (H. Sobotka), ^{ab}374
- Stryker, F. E., see Sobotka, Harry, *212
- Susceptibility to convulsions in relation to age, *4
- Sweating, studies of, on the mechanism of action of local antiperspirants, (Marion B. Sulzberger, et al.), ^{ab}364
- Sympathetic ganglion, the effect of histamine on an isolated, *149
- Synthesis of 1-dehydro-8-ionone, (H. Sobotka and J. D. Chanley), ^{ab}374
- TELLURITE**, potassium, reduction of, by living tissue (17369), (M. Wachstein), ^{ab}367
- Testosterone propionate, uptake of P³² in seminal vesicles of castrate rats after treatment with, *228
- Thiourea on mitosis in rat livers damaged by carbon tetrachloride, the effect of, *339
- Toxic agents, the influence of, on the female genital organs, a brief review, *333
- Transfer of drugs into the milk, *83
- Tribute to a lost world, *xiv
- Tuberculosis, renal, prognosis after nephrectomy for, (G. D. Oppenheimer and L. Narins), ^{ab}372
- "Two-step" exercise test, the Master, in the differential diagnosis of coronary artery disease, (S. Storch, et al.), ^{ab}372
- ÜBERTRAGUNG** sensibler Impulse im Rückenmark des Frosches, zur Frage der, *121
- Ueber die neurogene Appendicopathie, *30
- Umbreit, W. W., The mode of action of antibiotics: penicillin and streptomycin, *175
- Uptake of P³² in seminal vesicles of castrate rats after treatment with testosterone propionate, *228
- Use of dibenamine in pheochromocytoma and detection of pressor activity of the plasma by bio-assay, *320
- VERTEBRAL** bodies in sickle cell anemia, collapse of the, (W. A. Henkin), ^{ab}363
- Vitamin E in arteriosclerotic heart disease with electrocardiographic evidence, (M. E. Eisen and H. Gross), ^{ab}366
- WACHSTEIN**, M., The influence of experimental hydronephrosis and of several amino acids on the nephrotoxic action of dl-ethionine, *221
- Wagner, Richard, Problems in juvenile diabetes mellitus, *249
- Whooping cough, streptomycin in the treatment of, (Lewis Wanamaker, et al.), ^{ab}359
- Wirkung Elektrischer Hypothalamusreizung auf den Experimentell Erzeugten Bronchialmuskelkrampf, *10
- XANTHOMA** juvenile to systemic reticuloendotheliosis, the relationship of, *243
- ZAK**, Frederick G., Plumbism in children, *352
- Zak, Frederick G., see Adlersberg, David, *289
- Zellmembrandurchlässigkeit der Gelenkkapsel, Einfluss des Desoxycorticosterons und anderer Sterine auf die, *185
- Zur Frage der Übertragung sensibler Impulse im Rückenmark des Frosches, *121

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CONTENTS

	PAGE
OTOLOGY: ITS PRESENT STATUS. <i>Julius Lempert, M.D.</i>	381
THE WILLIAM HENRY WELSH LECTURE: FROM CLOSTRIDIUM WELCHII TO THE COXSACKIE VIRUSES: CHANGING MICROBIOLOGY. <i>Gilbert Dalldorf, M.D.</i>	396
ARTERIOSCLEROSIS AND DIABETES. <i>Ernst P. Boas, M.D.</i>	411
JUDICIUM DIFFICILE. A LESSON IN PERSPECTIVE. <i>Leo M. Davidoff, M.D.</i>	420
PERINEPHRIC AND RENAL CORTICAL ABSCESS DUE TO COLON BACILLUS WITHOUT BACTERIURIA OR PYURIA. <i>Kermit E. Ossermann, M.D., and H. Evans Leiter, M.D.</i>	424
SPONTANEOUS RUPTURE OF NORMAL GALL BLADDER DUE TO BILIARY TRACT OBSTRUCTION. <i>Alvin J. Kahn, M.D.</i>	428
ABSTRACTS	430

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OTOLOGY: ITS PRESENT STATUS*

JULIUS LEMPERT, M.D.

[New York]

Ever since Schwartze first described the simple mastoidectomy for acute suppurative mastoiditis and the Schwartze-Stacke Radical Mastoidectomy for otherwise incurable chronic middle ear suppuration, and up to the advent of sulpha-therapy and antibiotics in 1937, the practice of otology consisted mainly of the surgical treatment of a middle ear abscess and the complications resulting therefrom. During that period there were great contributions made in clinical diagnosis and histological studies of temporal bone disease which stimulated the progressive evolution of the surgical treatment of temporal bone infection and the various complications which often accompanied it.

Mount Sinai Hospital was immortalized in the history of otology because it had the great privilege of being the recipient of the distinguished services of Whiting, Libman and Friesner during that period.

Whiting was one of the great pioneering otologists of that day. He was the first to practice and advocate, in the face of great opposition, complete cell excision of the entire mastoid process even when the mastoid cell structure was found to be only partially diseased during the performance of a simple mastoidectomy. As evidence of the opposition this logical and simple advance of Whiting's met with in those days, I quote from his book, "The Modern Mastoid Operation," published in 1905 wherein he found it necessary to make the following statement in defense of his contributions:

"The antagonism which has been aroused against the most recent advances in the surgery of the mastoid region is simply an echo of former impotent protests which have since times forgotten, attended and invoked disaster upon every step of surgical progress in connection with procedures about the ear."

Emanuel Libman, one of the world's famous internists, and not an otologist, in addressing the 9th International Otological Congress in 1912 on the importance of blood cultures in the study of infections of otitic origin, made one of the great contributions to otology by calling attention to the fact that in lateral sinus thrombosis a positive blood culture is as a rule obtainable.

Isidore Friesner, a great clinician and otologic surgeon of that day, made a great contribution to otology with the publication of the Friesner and Braun book on Cerebellar Abscess of Otitic origin. Friesner was one of the few otologists of fame who was always willing to teach and impart his knowledge to others. Friesner, who personally was a conservative in otology, was nevertheless never known to have stood in the way of progress. Though he personally never performed any temporal bone surgery through the endaural approach, which I

* Delivered as the Isidore Friesner Lecture, Tuesday, April 24th, 1951, at the Blumenthal Auditorium, The Mount Sinai Hospital, New York City.

first described and employed, he nevertheless as associate editor of the Archives of Otolaryngology sponsored the publication of my manuscript on this subject. He personally sent it for publication to George Shambaugh, Sr., who was then Editor-in-Chief of the Archives of Otolaryngology. Shambaugh, in accepting for publication my manuscript entitled "Simple Subcortical Mastoidectomy," stated in his letter to me dated August 25, 1927, as follows:

"It represents the type of contribution for which we would like to reserve the Archives, that is an original piece of work."

The publication of this paper laid the foundation for the gradual development of today's new modern temporal bone surgery. The endaural approach to temporal bone surgery has been almost universally adopted since the advent of the antibiotics.

There were, prior to the antibiotic therapy period, a number of great otologists in the world and every big city could boast of otologists capable of doing good temporal bone surgery. However, the fact remains unfortunately that too many oto-rhino-laryngologists doing temporal bone surgery in those days were very poorly trained and some were doing this surgery without any training at all. The few greatly experienced and extremely capable otologists in each large community, outside of capably handling their own temporal bone surgery, were also acting as consultants, bystanders, trouble-shooters, and front men for the poorly trained and incompetent men who unfortunately were doing most of the temporal bone surgery. Those were what many of yesterday's poorly trained in otology oto-rhino-laryngologists refer to today as "the good old days" in otology. Those were "the good old days" when any one non-trained or poorly trained in temporal bone surgery would not hesitate to attempt this surgery since he was always able to blame the offending streptococcus for the unfortunate sequellae and poor surgical results, instead of his own incompetence.

Those were the days when after having accidentally injured the lateral sinus, instead of surgically controlling the bleeding and continuing to remove the pathologic process, everything within reach was packed into the mastoid wound to stop the bleeding, and the operation was called to a halt. The patient was sent back to his bed to await thrombosis of the lateral sinus, with the poor little streptococcus taking the blame for all the subsequent sequellae. Those were also the days when if the Facial Nerve was accidentally and blindly injured, the unoffending non-visualized Facial Nerve was accused of occupying the wrong and anomalous position within the temporal bone and reprimanded for having been in the pathway of the chisel. Such accidents often formed the basis for the publication of an article warning against such anomalies. Such publication often created a precedent for other articles alibiing many other unlucky men doing temporal bone surgery for the same kind of accident. Those were men doing temporal bone surgery who never knew that they injured the Facial Nerve unless the anesthetist called their attention to the facial paralysis. They always thought about the Facial Nerve, spoke about it, dreamed about it, but seldom saw the Facial Nerve while operating. When the anesthetist called their attention to the

fact that the face was crooked they surmised that they must have somehow and somewhere injured the Facial Nerve. Those were also the days when the Balance-Duell Operation for the repair of Facial Nerve injury was hailed as a great milestone of progress in otologic surgery. I personally looked upon the enthusiastic reception given the Balance-Duell Operation as a sad commentary upon the specialty of otology. This was a contribution mainly towards incompetent otology after having accepted badly performed temporal bone surgery as an irreversible fact. A much better contribution to otologic surgery, and especially toward humanity, would have been better training of temporal bone surgeons, so that Facial Nerve injury would become less frequent and when occurring the surgeon would know when, where and how it happened. With such understanding an accidental injury to the Facial Nerve is as a rule easily overcome immediately on the operating table and permanent facial paralysis is avoided.

Unfortunately those were the days when otologists were always taught ways and means of blindly avoiding injury to this or that anatomical structure while doing temporal bone surgery. They failed to train these men in the art of deliberately exposing to view all the surgical anatomy and thus decrease the danger of accidental injury to such anatomy.

Those were also the days when in doing temporal bone surgery, hearing function was often carelessly and unnecessarily sacrificed in the name of saving life. The conservation of hearing was seldom taken into consideration. Radical Mastoidectomies were performed and hearing function sacrificed when mastoido-atticotomies without sacrifice of the ossicular chain and the tympanic membrane would have sufficed for the removal of the pathologic process. Those were also the days when Radical Mastoidectomies were scheduled and reported, but very seldom radically performed. After opening the temporal bone and exposing to view the pathologic processes within it, they too frequently failed to remove the pathology for fear of injuring this or that anatomical vital structure which was lying hidden underneath the pathology.

In those pre-antibiotic days there existed neither medical nor surgical treatment which could possibly improve the hearing in those deafened as a result of otosclerosis. Nevertheless, oto-rhino-laryngologists fully cognizant of these facts unhesitatingly performed tonsillectomies and septum resections, used x-ray and radium therapy, gave hypodermic injections of all sorts of chemicals, fed patients all sorts of vitamins, inflated the eustachian tubes, massaged the tympanic membranes with electric percussors, etc., etc.; all this without ever improving the hearing in any of the patients. In defending such practice some of these men, in all sincerity, argued that the reason they treat these people with no hope of improving their hearing is solely because of their belief that one must not permit these people to lose hope of regaining their hearing. Furthermore, they piously stated that by treating these unfortunates they saved them from being victimized by quacks.

Those are the very same otologists who since the advent of the antibiotics, and in spite of the great advances in temporal bone surgery made possible by this advent, are spreading the gospel today that otology is finished. "It is no longer

what it used to be", they say. If the facts about much of yesterday's otology became generally known, everybody would say "Thank God, otology is no longer what it used to be."

Today young men in medicine, contemplating post-graduate study and preparation for the practice of oto-rhino-laryngology, are confused. They are being told that since the advent of the sulpha drugs and the antibiotics, oto-rhino-laryngology is a much contracted and limited in scope specialty. This, they point out, is especially true of otology. They are being warned that temporal bone surgery, which was so prevalent in the days prior to the advent of the antibiotics, is practically non-existent today. Strangely enough many of these young men, who are unfortunate enough to have served their internship in an institution whose chief in oto-rhino-laryngology thinks that way, cannot help but believe this to be true.

A careful, non-biased and frank analysis of the facts as they existed prior to the advent of the antibiotics, and comparison with the true facts which are responsible for less otologic surgery being done today in certain institutions, will reveal that the shortage today is not in surgical material but rather in surgeons who are properly trained to take advantage of the abundance of temporal bone surgery waiting to be done. The practice of otology, more than ever before, offers today a much wider field of usefulness to the properly trained otologist. Too many oto-rhino-laryngologists, who prior to the advent of the antibiotics, always found plenty of otologic surgery to be done are today doing little or no surgery. The reason these men are doing less otologic surgery is not because there is less to be done, but rather because today much of the otologic surgery these men practiced for years is no longer needed and the type of surgery in demand today requires special training which too few care to undertake.

With every new advance in temporal bone surgery the pendulum is not only retarded from swinging in the direction of further progress but is actually pushed in the opposite direction. Yesterday's ultra liberal temporal bone surgeon suddenly becomes the extreme conservative of today. Prior to the advent of the antibiotics, myringotomies were often unnecessarily performed by general practitioners, pediatricians and oto-rhino-laryngologists. Today almost none of them permit drainage of the infection to be established by paracentesis, even in the presence of clinical evidence of existing middle ear suppuration and bulging tympanic membrane. They employ antibiotics exclusively without establishing drainage. As a result of such treatment, recurrent attacks of otitis media are today much more frequent than they were when they were treated with incision and drainage alone. Functional testing of hearing in such cases has led me to believe that if normal hearing function is to be conserved in such ears, humanity would be best served if in addition to the use of the antibiotics, early drainage of the middle ear infection through a carefully placed and performed incision of the tympanic membrane by an otologist, would also be instituted. Whereas mastoidectomies were often performed too early instead of timely, today otologists treat suppurative mastoiditis with antibiotics without establishing drainage of the infection or removing the focus of infection. They convert the acute suppurative lesion into a subacute one and by repeating this antibiotic therapy with

each acute exacerbation they gradually convert the pathologic lesion into a chronic suppurative lesion with loss of hearing function as well. Humanity would be served best if in the presence of mastoid cell suppuration removal of the focus of infection would be instituted in addition to the antibiotic therapy. Chronic middle ear infections with cholesteatoma are being treated both locally and systemically with sulpha drugs and antibiotics year in and year out until labyrinthine fistulae form.

Today surgical treatment of temporal bone infection is considered superfluous by the otolaryngologist poorly trained in otology who does not like to assume responsibility for removal of pathology without having the streptococcus as an alibi for the sequellae of his surgical accidents. Even suppurative labyrinthitis, brain abscess and meningitis of otitic origin are being treated with the antibiotics and without searching for and removing the focus of infection. Such treatment is as a rule dangerous.

Though temporal bone surgery for middle ear infection and its complications has been largely reduced because of the advent of sulpha-therapy and the antibiotics, the antibiotics instead of sounding the death-knell of otology became the renaissance of the new modern temporal bone surgery. Labyrinthine surgery has been developed to a degree of perfection hitherto not dreamt of. A new and wide field in temporal bone surgery has thus been made available to the otologist. As a result of the gradual development of the Lempert Fenestra Nov-Ovalis Operation millions of people, deafened as a result of otosclerosis, can now have their hearing restored and permanently maintained thereafter.

This great advance in temporal bone surgery could not possibly have been reached were it not for the advent of sulpha-therapy and the antibiotics which permitted experimental surgery in the human without danger of postoperative infection. However this middle and inner ear surgery is technically so delicate that only those specially trained in this surgery can hope to do it successfully. Unfortunately there are not enough otologists today who are sufficiently trained to successfully do the constantly available tremendous amount of fenestration surgery. Many otologists have abstained from being trained in this new surgery because they felt that in many cases where a hearing improvement was originally obtained following the fenestration operation it was soon lost again because of osteogenetic closure of the newly created fenestra. This long existing obstacle to the permanent success of fenestration surgery has finally been removed.

THE PERMANENTLY PATENT FENESTRA NOV-OVALIS

Osteogenetic closure of the newly created fenestra following fenestration of the vestibular labyrinth for clinical otosclerosis has been the greatest deterrent to the permanent maintenance of the early hearing improvement obtained following this surgery. This has been recognized by otologists ever since this surgery has come into existence. This fact, though recognizable, was not surprising since it was natural to expect Nature to carry out its usual function of repair within the bony labyrinthine capsule just like it was expected to repair all the other surgically injured soft tissues.

We could hardly have expected Nature to repair all injured tissue without re-

pairing the newly created fenestra as well, since the identically existing constitutional biologic factors which govern repair following surgical injury in one type of tissue govern all types of injured tissue.

In recognition of this natural law of overall repair, in order to assure the permanent patency of the newly created fenestra we were for the first time confronted with the problem of experimentally seeking means and ways of preventing Nature from performing its naturally inherent duty of repair in the bony fenestra region without interfering with its mission of repairing the rest of the injured tissues.

With this mission in mind I decided to first observe and study how Nature repairs the newly created fenestra, how it closes it by osteogenesis and where the osteogenesis starts and ends in a post-fenestrated ear. I hoped thus as a result of the knowledge gained from such a study to perhaps be able to find means and ways of interfering with Nature's mission of repair and preventing osteogenesis either from starting or at least from completing its mission if its start could not be prevented. In all surgery Nature's law of repair is the greatest asset to the surgeon, but in fenestration surgery it is both the combined friend and enemy of the otologic surgeon. Here the surgeon expects the unnatural, he wants repair everywhere except within a bony area 2 mm. wide and 6 mm. long which is the fenestra gap created in the bony vestibular labyrinth. Isn't this asking too much of Nature?

What have I learned from the aforementioned study and how was this knowledge applied in an attempt to try and serve our purpose of keeping osteogenesis from taking place? I have revised 517 osteogenetically closed postoperative labyrinthine fenestras and studied the observations made in these fenestras. I learned therefrom:—

- 1) That bone-dust when left in the region of the fenestra stimulates and hastens its closure by osteogenesis. I therefore advocated that all bone-dust be meticulously removed (1).

- 2) That the most meticulous removal of bone-dust does not prevent ultimate bony closure of the fenestra. Fenestras created without the burr and therefore without formation of bone-dust closed as a result of osteogenesis as well.

- 3) That osteogenesis does not as a rule take place underneath the tympanomeatal flap on the outer surface of the bony labyrinthine capsule in the region surrounding the newly created labyrinthine fenestra.

- 4) That osteogenesis takes place underneath the tympanomeatal flap as a rule only intramarginally within the fenestra gap in the fenestra rim.

- 5) That osteogenesis of the fenestra rim as a rule begins within the innermost endosteal bony layer. However, I did not fail to realize that as far as the end result was concerned it made no difference whether the periosteal layer when not removed also regenerated or the enchondral layer left intact did not regenerate; neither would it make any difference if both of these bony histologic layers were removed to prevent them from participating in the osteogenetic process, since osteogenesis of the endosteal layer alone within the fenestra rim is sufficient to result in fenestra closure.

In the hope of preventing osteogenesis within the endosteal layer of the fenestra rim I advocated burnishing the fenestra rim with a gold burnishing burr which was proven experimentally in the animal to delay osteogenesis but not to prevent it (2). As a result of further experimentation with burnishing the fenestra rim with various metals I found that burnishing the fenestra rim with lead in two Rhesus monkeys prevented osteogenesis (3) and used lead-burnishing of the human fenestra rim since. However despite the fact that the percentage of closures was reduced since its use I never knew which fenestra would remain open and which one would not.

Furthermore, I was never able to prove to myself or anyone else that the fenestra which remained open did so because of having been burnished with lead. Also was I not unmindful of the fact that many fenestras which I did not burnish with lead remained open as well. Nor did I overlook the fact that many otologists who were not using lead were also rewarded with a fair percentage of permanently open windows following this surgery. However, they also were unable to prove to either their own or anybody else's satisfaction why these fenestras remained patent while other fenestras which they made with the same technic closed by osteogenesis.

I succeeded in preventing bone regeneration within the fenestra rim by physically impeding osteogenesis with metal obturators. However, I found it technically difficult to make a fenestra which could be snugly fitted with a prefabricated prosthesis (4). To make a prosthesis to individually fit each newly created fenestra was found not to be practical. I found that I could improve hearing and prevent osteogenesis within the fenestra rim with a properly inserted mobile cartilage stopple (5). However in a large percentage of cases the ultimate formation of fibrous tissue between the fenestra rim and the stopple eventually rendered the stopple immobilizable by air-borne sound, and I had to abandon the use of the cartilage stopple.

6) I have learned that osteogenesis took place less frequently in the region nearest the ampulla of the external semicircular canal. I thought this was so because the fenestra was as a rule wider in this region. As a result of this observation I developed and described in 1941 the Fenestra Nov-Ovalis Technic (4) whereby a much wider fenestra is created in the surgical dome of the vestibule. This new technic was universally adopted since. Otologists employing the Fenestra Nov-Ovalis Technic have since observed and reported a much larger percentage of permanently patent fenestras than following their use of my originally described one-stage technic whereby the fenestra was created in the narrow portion of the external semicircular canal posterior to the ampulla. However, this universal observation has nevertheless failed to explain why and how some fenestras made with my originally described one-stage technic (6) which could not be made as wide and were much narrower remained permanently patent. It also failed to explain why, despite the use of the Fenestra Nov-Ovalis Technic, about 30% of the fenestras closed nevertheless as a result of osteogenesis.

7) I learned that osteogenesis sometimes takes place within the perilymph

space, due to bone chips unavoidably lost within it following the pulverization of the bony endosteal layer of the labyrinthine capsule. As a result of this knowledge gained I have developed and since employed the Bone-Dust-Free Cupola Technic (7) for creating the fenestra. Bone-dust no longer being formed with this technic, the problem of its removal has been done away with and perilymphatic osteogenesis can thus be avoided. However, this bone-dust-free technic was not expected to and does not prevent osteogenesis from taking place in the freshly injured fenestra rim margins.

In summarizing my aforementioned study of osteogenetic fenestra closure and the problem of its solution, it is not difficult to see that despite the fact that I have learned much about how a newly created window closes as a result of osteogenesis and succeeded in greatly reducing the percentage of closures by developing and employing the Fenestra Nov-Ovalis Technic I nevertheless failed to learn therefrom:—

1) Why osteogenesis was prevented from taking place in a much larger percentage of ears following the use of the Fenestra Nov-Ovalis Technic?

2) Why osteogenesis was not prevented from taking place in all the fenestras following the use of the Fenestra Nov-Ovalis Technic?

3) Whether the creation of a wider fenestra was the sole reason for the prevention of osteogenesis in these patients whose fenestras remained patent or was it only a contributory factor to its prevention by some other still unknown main factor?

4) What was the main factor without the existence of which osteogenesis could not be and was not prevented within the fenestra rim even in the presence of a wider fenestra?

5) When osteogenetic repair took place why did it do so only intramarginally within the fenestra gap in the fenestra rim and not extra-marginal to the fenestra gap outside the fenestra rim, regardless whether the fenestra was made wide as in the Fenestra Nov-Ovalis Technic or narrow as in the originally employed one-stage technic?

Since some windows closed and others remained open with the use of all the known to me media employed for the prevention of osteogenesis, it occurred to me that perhaps none of these media are capable of preventing it and that some other as yet non-identified factor is at work when osteogenesis is prevented. Though osteogenesis was prevented from starting in a much greater percentage fenestra rims following the use of the Fenestra Nov-Ovalis Technic, I was nevertheless not convinced that making the fenestra wider was the sole reason for preventing the start of osteogenesis within the freshly injured rim margins of the fenestra gap in a much larger percentage of postoperative fenestras than heretofore obtainable in narrow fenestras. I could envisage that a wider fenestra may occasionally not complete its mission of fenestra closure after osteogenesis started but could not understand why the creation of a wider fenestra should prevent osteogenesis from starting in its freshly injured fenestra rim.

It therefore occurred to me that the same still non-identified factor which prevented osteogenesis in some of the narrow fenestras was most likely also the

one which prevented it in the wider fenestras. Perhaps the reason why more of the wider fenestras stayed open was because a wider fenestra favored this main factor more frequently. I still further reasoned that if there is such a factor, and if a wider fenestra favors the prevention of osteogenesis by this factor, then why did it not prevent it in every one of the fenestras created with the Fenestra Nov-Ovalis Technic? This suggested further that perhaps this unknown to me factor did not always exist and in its absence bone regeneration did take place.

To seek an answer to these questions I had to resort to studying the permanently patent fenestra following the Fenestra Nov-Ovalis Technic and also following my originally first described technic to see if the same factor prevails in both technics. I thought that by studying the fenestra gap and rim of the permanently patent fenestra I may be able to recognize and observe some factor still unknown to me which may be held responsible for the prevention of osteogenesis in the fenestra rim. I also hoped that the findings in the fenestra gap of the patent fenestra may perhaps also lead me to the recognition of the factor responsible for the consistent prevention of osteogenesis outside the fistula.

I investigated the fenestra region in 100 ears which failed to show improved hearing following fenestration in order to observe if possible how osteogenesis was prevented from taking place in some of the fenestra rim margins and why it was not prevented in the others. I wanted to see if there is any difference outside of observable osteogenesis between a closed and an open window.

After studying 100 postoperative fenestras of ears which failed to show improvement in hearing following the Fenestra Nov-Ovalis Operation, I found 28 of them closed by bone regeneration and 72 fenestras having remained permanently patent because bone regeneration did not take place. In the 28 osteogenetically closed fenestras the findings were the same as in the 517 previously examined closed fenestras. The flap was readily lifted and separated from its attachment to the outer surface of the fenestrated region. No bone regeneration has taken place in this region. The fenestra gap was found to be obliterated by newly regenerated bone. The inner surface of the entire flap was found to be evenly smooth as it was when originally placed to cover the fenestra region (fig. 1). This held true whether fenestra region was gold burnished or lead-burnished or not burnished at all.

In every one of the 72 fenestras which remained patent because osteogenesis did not take place, either extramarginal to the fenestra rim or intramarginally in the rim of the fenestra gap, the following significant differentiating observations were made: The tympanomeatal flap was found to be not only adherent to the bony labyrinthine capsule extramarginal to the fenestra gap, but the inner surface of the portion of the flap facing the fenestra gap was found to be invaginated into the fenestra gap and adherent intramarginally to the bony fenestra rim. After slowly and gently separating the flap from its adhesion intramarginally to the bony fenestra rim and lifting it from the entire outer surface of the bony capsule extramarginal to the fenestra gap, a moulded impression of the fenestra gap was observed to exist on the inner surface of the tympanomeatal flap in every one of the 72 patients in whom the fenestra re-

mained patent (fig. 2). The membranous labyrinth which was apparently not adherent to the flap remained undisturbed in its position within the perilymph space. In other words, whenever invagination of the flap into the fenestra gap and intramarginal adhesion of its inner surface to the bony fenestra rim was observed to have taken place, osteogenesis within the bony fenestra rim was prevented and permanent patency of the fenestra resulted (fig. 3). On the other hand, whenever the flap was observed to have become adherent outside the fistula but failed to have become invaginated into the fenestra gap and adherent

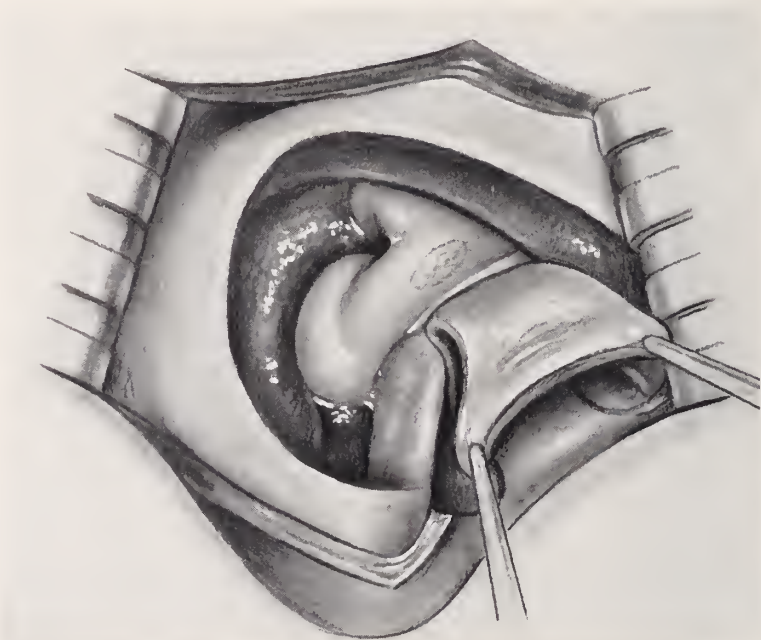


FIG. 1. Smooth inner surface of tympanomeatal flap as seen during revision of every osteogenetically closed fenestra.

to the fenestra rim, osteogenesis was prevented only outside the fistula and not in the fenestra rim (fig. 4).

The aforementioned observations led me to the conclusion that no matter what I heretofore did or did not do to prevent osteogenesis from starting in the fenestra rim and eventually closing the fenestra gap following the fenestration operation, unless invagination of the flap accidentally took place and its inner surface became adherent to the fenestra rim within the fenestra gap, osteogenesis did take place and closed the fenestra gap.

The ultimate fate of the newly created fenestra was non-predictable because osteogenesis evidently was only prevented whenever the pressure exerted by the mastoid wound packing accidentally happened to be sufficient to result in invagination and adhesion of the flap to the fenestra rim.

As a result of these findings it became obvious that: 1) The bony fenestra edge

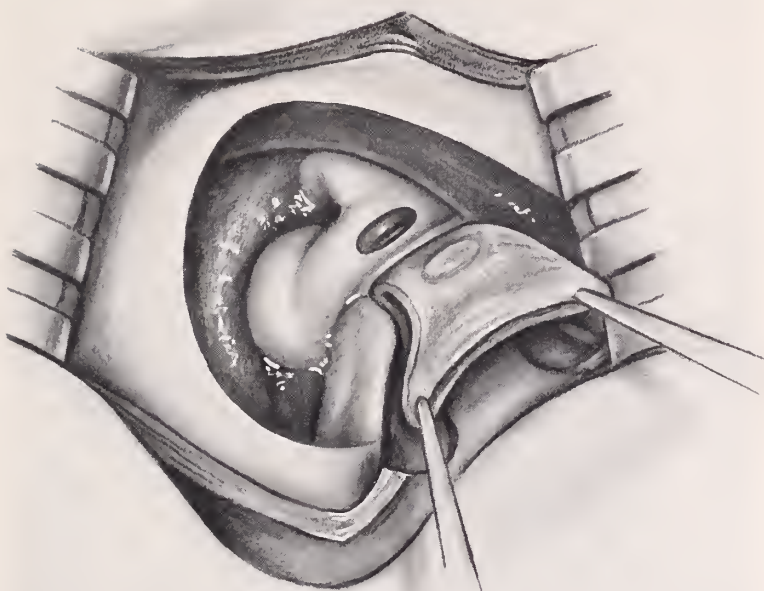


FIG. 2. Moulded impression of fenestra gap on inner surface of tympanomeatal flap as seen during revision of every permanently patent fenestra.

Intramarginally invaginated skin flap

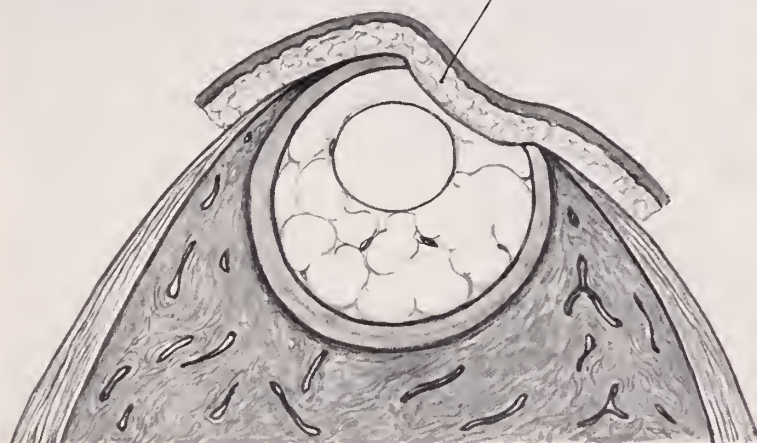


FIG. 3. Diagram showing cross-section of permanently patent fenestra. Whenever the inner surface of the tympanomeatal flap became invaginated into the fenestra gap and became adherent to the lateral walls of the fenestra rim osteogenesis was prevented intramarginally within the fenestra rim and fenestra remained permanently patent.

or rim can heal either by osteogenesis which obliterates the fenestra or will heal by invagination of the inner surface of the flap into the fenestra gap and its adhesion to the bony edge of fenestra rim, which prevents osteogenesis and permits fenestra to remain patent; 2) more windows stayed permanently open with the use of the Fenestra Nov-Ovalis technic because the much wider fenestra created with this technic favored accidental invagination of the flap into the fenestra and its adhesion to the fenestra rim much more frequently than the previously made much narrower fenestra; 3) osteogenesis as a rule did not take place extramarginal to fenestra rim because adhesion of the flap to the bony labyrinthine capsule outside the fistula prevented it.

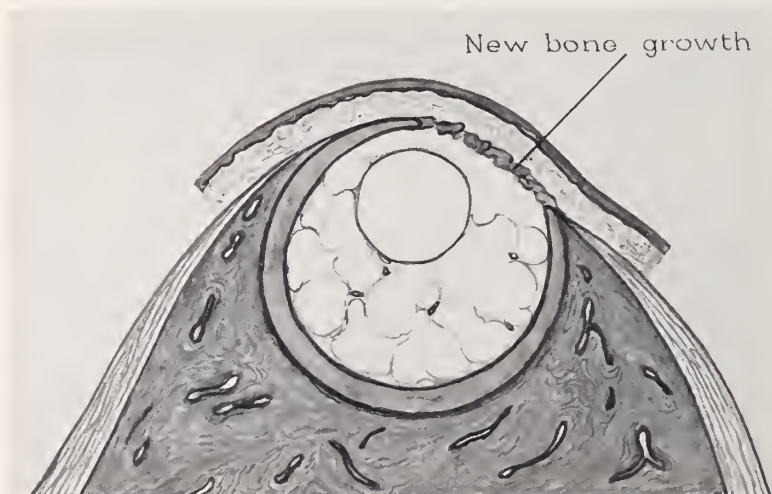


FIG. 4. *Diagram showing cross-section of osteogenetically closed fenestra.* Whenever the inner surface of the tympanomeatal flap did not become invaginated into the fenestra gap and it did not become adherent to the lateral walls of the fenestra rim, osteogenesis started intramarginally within the fenestra rim and eventually closed the fenestra gap.

Invagination and adhesion of the flap to the bony fenestra rim is undoubtedly the scientifically correct and logical solution for the prevention of osteogenesis of the fenestra rim. This should be obvious to any otologist of experience who could not have possibly failed to observe that the permanent postauricular fistula following the postauricular mastoidectomy is also the result of invagination of postauricular skin into the mastoid cavity and adhesion of its inner periosteal surface to the bony edges of the severed outer mastoid cortex. When the postauricular skin and periosteum following mastoidectomy healed by primary union the outer mastoid cortex as a rule regenerated underneath it and fistula was thus prevented. When the postauricular skin failed to heal by primary union as a result of postoperative infection it often became invaginated and adherent to the bony edges of the mastoid cortex and a permanent postauricular fistula resulted (fig. 5).

How can we now, with this new knowledge gained about the prevention of osteogenesis, consistently and deliberately create a permanently patent fenestra?

- 1) Make fenestra on surgical dome of vestibule.
- 2) Make it as wide as possible. In order to do so you must remove the antero-lateral wall of the ampullated end of the bony external semicircular canal, thus exposing a wider area of the perilymph space anterior to the normally placed



FIG. 5. Invagination and adhesion of postauricular skin and periosteum to bony edges of severed outer mastoid cortex as seen in every postauricular fistula.

membranous labyrinth. Fenestra should be about 2 mm. wide and about 6 mm. long.

3) Place tympanomeatal flap so that it covers and contacts the entire bony region outside the fenestra gap.

4) Invaginate that portion of the tympanomeatal flap which faces the fenestra gap, sufficiently only to contact intramarginally the fenestra rim (fig. 6).

5) Place a cotton inlay moistened in Ringer's solution over the invaginated portion of the tympanomeatal flap and mould it so that it forces the inner surface

to contact and stay in contact with the fenestra rim edges intramarginally. This favors its adhesion intramarginally to the bony fenestra rim (fig. 6).

6) Secure and hold cotton inlay in its position with a piece of paraffin mesh gauze mould over it.

7) Pack rest of cavity with paraffin mesh gauze to hold the initial packing in its position.

8) Remove all packing except the first piece on sixth or seventh day.

9) Remove last piece on 10th-12th day.

I have finally observed and learned that invagination of the tympanomeatal flap into the fenestra gap and intramarginal adhesion of its inner surface to the relatively avascular bony fenestra rim prevents osteogenetic closure of the

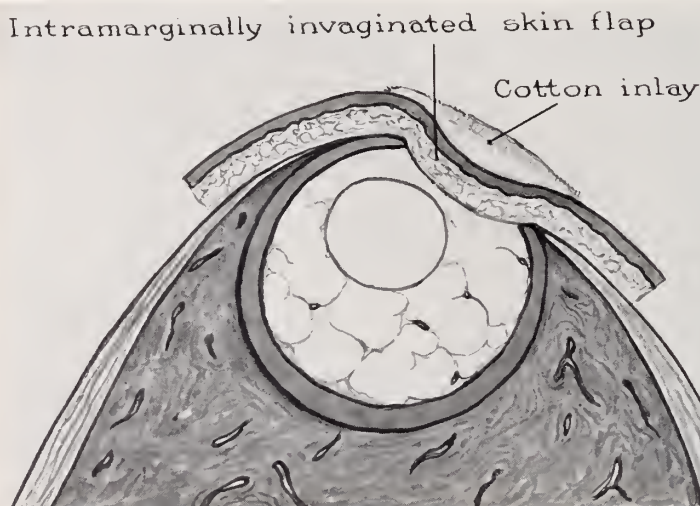


FIG. 6. Cross-section diagram demonstrating how to accomplish invagination of the tympanomeatal flap into the fenestra gap and the adhesion of its inner surface intramarginally to the fenestra rim for the prevention of osteogenetic closure of the fenestra nov-ovalis.

newly created fenestra. As a result of this observation it also became obvious that the reason osteogenesis did not as a rule take place in the relatively avascular bony labyrinthine capsule outside the fistula following fenestration surgery even when osteogenesis took place within fenestra rim was because the flap which became adherent to it prevented it. With this knowledge at hand we should now be able to deliberately prevent postoperative osteogenetic repair of the Fenestra Nov-Ovalis and obtain as a result a much larger percentage of permanently patent fenestras than ever before.

CONCLUSION

Otology, like ophthalmology, will first come into its own and take its place as the great and expanded specialty which it has become since the advent of the antibiotics when it will, like ophthalmology, free itself from the combination of oto-rhino-laryngology and become an independent specialty. Just as long as

otology will be a part of oto-rhino-laryngology, because of it being the most difficult part of the combined specialty to master, its progress will be hampered by those oto-rhino-laryngologists who remain poorly trained in otology. The same held true years ago when the general surgeon insisted upon doing brain surgery. Its progress remained impeded until the general surgeon was willing to recognize the fact that the specially Cushing-trained brain surgeon can do this surgery with much better results.

I know that what I propose is very much contrary to the general opinion of the oto-rhino-laryngologists. They are not only seeking to keep the three specialties combined but are also seeking to embrace and encroach upon other surgical fields. Time will, however, definitely prove that they are wrong. The practice of otology is today a full-time job. What is expected today of the surgeon is not more types of surgery, but rather better surgical results.

Whiting, in his book "The Modern Mastoid Operation", published in 1905, stated as follows:

"Greater confidence is now reposed in the operator and the present higher standard of professional intelligence demands the exhibition of greater skill at his hands."

This lament of Whiting's is much more timely today than it was then.

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THE WILLIAM HENRY WELCH LECTURE*
FROM CLOSTRIDIUM WELCHII TO THE COXSACKIE VIRUSES:
CHANGING MICROBIOLOGY

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The preparation of this lecture proved to be a very pleasant task . . . thanks to William Welch. I reread the Flexners' biography and a number of Welch's bacteriologic studies. I gossiped with older friends who had known him. I recalled the vivid recollections my old chief, James Ewing, had of Welch's early work, in New York. I had a fine time thinking about Welch and how the Cocksackie viruses, which I had agreed to discuss, could be related to him. I thought of the changes that had taken place in bacteriology in the past fifty years, the new sciences of immunology and virology, of experimental epidemiology as developed by Topley and Webster, of chemotherapy. And I realized that of the two aspects of the Cocksackie viruses that I most wanted to discuss, the things that seem to me to be "good to know and worthy to be told", one represents a new conception of the infectious diseases and the other, a new approach to an old problem, a problem Welch dealt with frequently and successfully. All the more reason, perhaps, to include it in a Welch lecture. And so I decided to tell you what we know of the Cocksackie viruses as agents of disease and what may be their ecological significance. But first, as introduction, I should tell you what we know of the viruses themselves.

The Cocksackie viruses constitute a group of filterable agents that are most often found in the feces of young children. We might call them enteric viruses and the Cocksackie group might be compared with the salmonella group of bacteria.

They are sources of very common human infections. This has been proven by several extensive tests of population groups and is borne out by the age distribution of patients, most of whom are children. Epidemiologists assume from such a distribution of cases by age groups that adults are immune and must therefore have been more or less universally infected. Considering the number of immunologically distinct types of Cocksackie viruses that have already been distinguished—fourteen have been identified in my laboratory alone—this implies an extremely high attack rate among the young. Perhaps we should question the assumption that adult immunity is acquired through infection. Mice become resistant as they mature, without immunization. But in the case of man the assumption is supported by the fact that adult serum usually does contain antibodies for a number of Cocksackie viruses.

* Delivered at the Blumenthal Auditorium, The Mount Sinai Hospital, New York, N. Y., February 13, 1952.

The Cocksackie viruses are among the smallest of the known viruses. Their diameter is probably about the same as that of poliomyelitis virus. Both freely pass Elford membranes with average pore diameters of 34 m μ . We still do not know what they look like for neither Cocksackie nor poliomyelitis viruses have been positively identified in the electron microscope. Normal tissues contain particles of their estimated size and we have so far failed to separate the normal components and purify the virus so that we can be sure what we are seeing.

They are surprisingly stable. Suspensions remain infective after standing for a week on the laboratory bench. Original specimens that have been stored for years in the dry ice chest seem to have lost none of their activity. Those types that have been tested have all been highly resistant to changes of pH and to heat. Neither cresol nor ether inactivates them; the cresol jar in which instruments are stood may become an infective inoculum.

As far as we know, they occur only in man, and, in man, only during the late summer months. At such times they have also been found in sewage and on flies. They are said to infect cockroaches which for a time become carriers but no naturally infected cockroaches have as yet been found. Our own experience in New York suggests that a succession of distinct types accounts for the sequence of epidemics, each of which is self-limited.

In all these respects, the Cocksackie viruses are similar to poliomyelitis virus and it is difficult to discuss them without referring to poliomyelitis. On the other hand, they may be distinguished from poliomyelitis virus on the basis of host range and experimental lesions. The Cocksackie viruses have a questionable pathogenicity for monkeys but are highly pathogenic for infant mice. Poliomyelitis viruses are, of course, fully pathogenic for monkeys and, when pathogenic at all for mice, spare the young and paralyze the adults. Poliomyelitis virus seems to traverse the nerves and destroy motor cells in a rather characteristic pattern. The Cocksackie viruses, in experimental animals, have a broader tropism including an affinity for striated muscle, fat, and the brain. Some paralyze by destroying the muscle rather than the nerve cell. The varieties that do attack the brain characteristically strike hardest at the cerebrum and midbrain and the signs are predominantly those of upper rather than lower motor neurone destruction. Among last year's strains were two that cause lesions of the motor neurones, chiefly in the medulla. An occasional focus of anterior horn cell destruction has been noted with other types. These lesions resemble somewhat the effects of poliomyelitis virus infection.

Morbid anatomy has become a cornerstone of our knowledge of the Cocksackie viruses. The lesions and the unique susceptibility of immature mice are the two criteria by which they may be recognized; the lesions also identify two distinct groups in the Cocksackie family, Groups A and B (1). Group-A strains induce lesions only in striated muscles; the group-B strains destroy fat and the brain as well as muscle. The groups differ in other respects. The signs of infection in mice reflect the pathologic picture and are quite different. Group-A strains are more easily isolated and worked with. And what is of greater medical inter-

est, the groups have clinical significance. The simplest way to summarize what we know of the pathogenicity of the various Cocksackie viruses and the two groups is to review several of the more instructive studies.

The original strain is now known as serologic Type 1 of Group A. It was isolated from feces collected from two boys who at the time had typical symptoms of paralytic poliomyelitis. Both boys responded immunologically to Type 1 during convalescence. Poliomyelitis virus was demonstrated in the same fecal specimens that had yielded the Cocksackie virus (2). Three other outbreaks of Type-1 infection have since been studied in which the circumstances were very similar to those in the village of Cocksackie. The largest epidemic, in Easton, Pennsylvania, included 47 hospitalized patients all but 9 of whom were paralyzed. Many of the patients were examined for the presence of both poliomyelitis and Cocksackie viruses. Seventy-five percent (27 of 36) were found to be infected with poliomyelitis virus and 64 per cent (27 of 42) were excreting Cocksackie virus. Of the 28 isolated strains, 24 were Type 1 (3).

Nassau County on Long Island had a rather severe outbreak of poliomyelitis in 1949. We recovered Type 1 Cocksackie virus from three patients. Two of these were severely paralyzed. Other Group-A types were isolated from Nassau patients who made uneventful recoveries (4). Independently, Curnen and Melnick examined specimens from 20 patients who lived in New York City. From 2 they isolated Cocksackie virus. Both strains proved to be Type 1 and both patients were paralyzed (5). Thus the record regarding Type 1 is that every proven outbreak associated with poliomyelitis has been remarkable because of the frequency and severity of paralysis. On the basis of the Easton epidemic, Melnick suggested that Cocksackie virus infection enhances the malignancy of poliomyelitis (6). The evidence of all four outbreaks appears to support his view which should however be qualified because the coincidence holds only for Type 1 of Group A. Epidemics associated with Group-B viruses have been relatively free of paralysis and one epidemic in which Type-2 Group A virus predominated was also unusually benign (7).

During the summer of 1948 we collected specimens from patients in many parts of New York. Some of these yielded Cocksackie viruses similar to the original strain in their behavior in mice although they were antigenically different. From 8 specimens the second variety of Cocksackie virus was isolated, the one we speak of as Group B. Surprisingly, none of these 8 patients had been paralyzed although their physicians had considered them probably cases of poliomyelitis. The 8 strains proved to be identical and represent serologic Type 1 of Group B. This type has not been found again in New York. During 1948 it was evidently widely prevalent in Connecticut as well as New York. Curnen recovered the same strain from 6 of 14 fecal specimens and demonstrated the presence of antibodies in each of 10 serum specimens. None of his patients was paralyzed, but one had symptoms suggestive of epidemic pleurodynia and when, somewhat later, he observed a number of infections among laboratory workers, he noted that 4 of the 6 also had symptoms of pleurodynia (8). The same virus was later implicated in a small epidemic among the staff of the Rockefeller Hospital. Two

of these cases suggested epidemic pleurodynia (9). British physicians have also claimed a relationship between Cocksackie virus infection and Bornholm disease (10), a relationship that has now been confirmed on numerous occasions. Boston's 1947 epidemic of pleurodynia yielded Cocksackie viruses (11). Gard, investigating a Swedish epidemic, isolated Group-B virus from roughly a third of the patients (12). During the summer of 1951 pleurodynia was prevalent in Texas and also in many parts of Great Britain. Correspondents report the frequent isolation of Cocksackie viruses (13). As far as I can determine, only Group-B strains have been consistently associated with epidemic pleurodynia and the evidence has seemed to us a rather impressive demonstration of the importance of distinguishing between the two varieties. Bornholm disease is evidently a consequence of Group-B Cocksackie virus infection. We must anticipate, however, that Group-A strains may some day be isolated from such cases because double infection is not a rare occurrence and because it is difficult to identify a Group-B virus in a specimen that also contains a Group-A strain.

Doubtless many members of this audience are more familiar with epidemic pleurodynia or Bornholm disease than I am but do you remember that in 1937 Madsen demonstrated that Bornholm disease and poliomyelitis have identical season distributions (14) (fig. 1) and de Rudder postulated that the agents responsible for the two were probably closely related? De Rudder summarized the similarities between the two diseases: the muscle pains, changes in the cerebrospinal fluid, fever curve, seasonal occurrence, association with places, geographic distribution, and the apparent tendency of both to spread by jumps. Epidemic myalgia, he wrote, is a pathomorphie variant of poliomyelitis (15).

Huebner and his colleagues have identified a second disease as a result of Cocksackie virus infection (16). During repeated testing for the viruses among the residents of a Washington suburb they encountered an outbreak of herpangina. More than 80 per cent of the patients were found to be infected with Group-A strains. Herpangina is a characteristic, benign summer disease that was originally described by Zahorsky in 1920. Clinical diagnosis rests on the presence of minute, herpetiform lesions of the soft palate, tonsillar pillars, and posterior pharynx. The gums are not involved. It is a disease of children; only one of Huebner's patients was an adult. Last summer, for the first time, we were able to test cases of herpangina and succeeded in isolating viruses from each of three patients. Herpangina is presumably a result of Group-A infection. Whether all Group-A types—there are already at least 10—may cause it remains to be proven. Huebner implies that only particular types are responsible. In view of our experience with Group-A strains in the laboratory, we are disposed to agree with him in principle. We find significant biologic differences between the Group-A strains as well as individual antigenic characteristics. For example, the Group-A types differ in their ability to multiply in eggs and in tissue culture.

Thus the circumstantial evidence we have implies that Group-B Cocksackie viruses bear an etiologic relationship to epidemic pleurodynia and that at least certain Group-A types are etiologically related to herpangina. It is perhaps an

unsatisfactory kind of evidence but there is plenty of it. In truth, we have but incompletely satisfied only the first of Koch's postulates that the parasite occur in every case of the disease in question and under circumstances that account for the pathological changes and clinical course. Koch also demanded proof that it occur in no other disease in a fortuitous manner, that it be isolated and repeatedly grown in pure culture, and thereafter be shown to induce the disease anew.

Considering the regularity with which Group-A infection has been shown to be associated with herpangina and that an intimate if less regular association

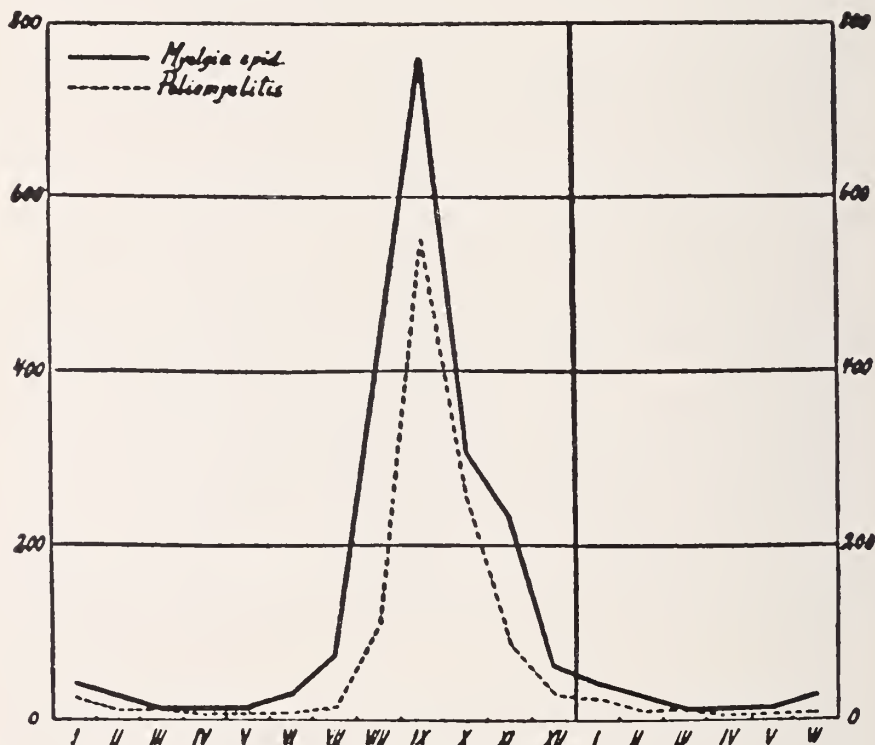


FIG. 1. Seasonal incidence of epidemic myalgia and of poliomyelitis in Denmark, 1931-1935. (Reproduced from: Madsen, Thorvald, Lectures on the epidemiology and control of syphilis, tuberculosis, and whooping cough, and other aspects of infectious disease. The Abraham Flexner Lectures; Series No. 5, Baltimore, Williams and Wilkins, 1937, p. 136.)

of Group-B strains and pleurodynia has occurred in many parts of the world, we may have met Koch's first requirement as fully as is possible. The relative infrequency with which Group-B strains have been isolated may be a result of the difficulties in adapting these varieties to mice. Furthermore, in the case of Bornholm disease we have proof of Koch's fourth postulate in Curnen's laboratory infections. Koch's second postulate was formulated before the healthy carrier had been recognized. His third requirement is not applicable to virus disease for viruses cannot be grown in pure culture. They are biologically incomplete in the absence of living cells.

It seems to me that Huebner has made a significant contribution to the problem in urging that the isolations of Cocksackie viruses be controlled by testing comparable groups of healthy individuals. It is true that Koch was aware of this point for he required, as I have said, evidence that the agent does not occur in other diseases in a fortuitous manner. Huebner's position is an extension of this principle aimed to control the influence of the healthy carrier. He has applied the principle in the modern, statistical manner. Truly, microbiology has changed in the degree it has accepted mathematical tests of significance although I find many of these tests of uncertain importance. Thus while Huebner and his associates have questioned whether Cocksackie viruses have so far been proven to be the cause of any disease other than herpangina (17), for which they have adequate studies of controls, it seems to me that the repetition of the association of Group-B viruses with pleurodynia in various countries and at different times, if not adaptable to statistical analysis, is nevertheless quite conclusive by the rules of common sense.

Some years ago Rivers undertook to modify Koch's postulates to meet the needs of virologists (18). He urged that we try to prove an association between the disease and an immunologic reaction to the virus in question. Rivers had largely relied on such evidence in proving the viral etiology of lymphocytic choriomeningitis. Unfortunately this criterion casts little light on the part of the Cocksackie problem that lies in the darkest shade for it does not meet the problem of dual infection. The development of antibodies proves that infection has taken place but nothing more. How then shall we prove the disease provoking properties of the Cocksackie viruses?

It would be most helpful if we learned to recognize the lesions of Cocksackie virus infection in man and correlated them with the presence of virus. As a morphologist I find it difficult to believe that such distinctive agents do not induce rather characteristic tissue changes. The demonstration of an association between the pathogen in question and its lesion has in the past been of the utmost importance in establishing the etiology of infectious diseases. Koch recognized its importance in the lecture in which he listed the four postulates (19). He called attention to the special significance of typhoid bacilli isolated from the spleen rather than from the intestinal contents. His advice, what might be called Koch's fifth postulate, has unfortunately been much neglected.

A bacteriologist friend asked me: "What do you think would have happened if Landsteiner had had your patients instead of his and had inoculated suckling mice instead of monkeys?" It is idle speculation. Landsteiner would not have gone astray, because he tested spinal cord, not feces. His proof of the viral etiology of poliomyelitis was based on the observation that an aqueous extract of diseased cervical cord was capable of inducing poliomyelitis lesions in monkeys. Landsteiner did not require surveys yet his proof was conclusive. It has survived without challenge for more than forty years.

Welch relied on similar proof, perhaps because he, too, was first of all a morbid anatomist and experimental pathologist. I find his bacteriologic studies are strongly colored by the pathologist's point of view. Welch's discovery of the

gas bacillus, for example, was the result of an effort to explain the formation of gas in the great vessels post-mortem, a lesion seen only in the dead house. His study of the pneumococcus is an example of the significance of the lesion. The pneumococcus was first discovered by Sternberg and later by Pasteur; Sternberg in his own saliva, Pasteur in the saliva of a human case of rabies. Pasteur called it the coccus of "sputum septicemia" because it produced septicemia in rabbits. Fraenkel and Weichselbaum later associated it with lobar pneumonia and Welch supported their conclusions. Welch found a relationship between the organism and the lesion of croupous, or fibrinous pneumonia. He related it not only to this special kind of pneumonia but to the evolution of the lesion. Welch was also correct about the diphtheria bacillus because he recognized the significance of the diphtheritic membrane in the throat. Most effectively, it seems to me, he combined anatomical and bacteriologic observations, tested them critically, distilled them gently with the warmth of his excellent judgment, and found the correct answer.

The need for sharper criteria of Cocksackie virus infection may be less acute in the case of herpangina and epidemic pleurodynia because clinically both are unusually distinctive. But other symptoms are associated with Cocksackie virus infection, which are relatively ambiguous. Sometimes these symptoms occur in the course of herpangina and pleurodynia, sometimes alone. For example, Zahorsky was puzzled by patients who had severe headache and pains in the neck (20). He sometimes suspected poliomyelitis and wrote: "The impression is accentuated by the tenderness of the extremities on movement." An epidemic of encephalomyelitis characterized by unremitting headache, stiffness of the neck and back, photophobia and retrobulbar pain, occurred in Tennessee in 1946. Many of the patients had herpetiform lesions in their throats. The description of the lesions matches that of herpangina (21). Were these cases due to Cocksackie virus infection? Central nervous system involvement has also been noted in patients with Bornholm disease. Tasker Howard called attention to it during the 1942 outbreak in Brooklyn (22). McConnell found 3 of 16 nurse patients had cerebral symptoms (23). Gsell described a special form of the disease as "meningitis myalgica" (24). Neurologic complications were reported during last summer's epidemic in Great Britain (25). I am told that very severe symptoms characterized the recent cases in Switzerland (26).

Should we suspect these to be cases of dual infection, as the paralyzed patients are presumed to have been, or are certain strains of Cocksackie virus more neurotropic than others? It was early reported that Cocksackie virus had been isolated from the brains of fatal cases of poliomyelitis (27). Unfortunately the lesions were not described and the validity of the isolations has since been questioned. However, Doctor Lennette tells me that he has succeeded in one instance in recovering a Cocksackie virus from a human brain (28) and Sven Gard reports a specimen of cerebrospinal fluid that contained a Cocksackie virus (29). We must reserve judgment for a time on the degree of pathogenicity of the Cocksackie viruses.

The problem is a lively issue for another reason. It has been suggested that the Cocksackie viruses be considered members of a family or tribe of poliomyelitis

viruses that would also include the so-called EMC viruses. In justification it is noted that the three viruses are similar in size and in the lesions they cause in experimental animals. For example, the EMC viruses induce lesions of the skeletal muscles that are in detail identical with those associated with Cocksackie virus infection. They also cause poliomyelitic lesions of the brain and cord. I believe the suggestion is premature but not without virtue. It reminds me of a statement of Jacob Henle (30). Henle, more than a hundred years ago, wrote a remarkable forecast of the bacteriology that was then not yet born. In it he predicted, for example, the kinds of evidence that would be required to prove the bacterial nature of a disease. Koch was Henle's student and Koch's postulates are thought by some to represent Henle's views. In his remarkable essay Henle wrote: "Diseases resemble one another, because their causes resemble each other." It is a principle that has stood up well throughout bacteriology and promises to be as true of the virus diseases. It may be, therefore, that future workers will find further similarities between poliomyelitis and Cocksackie virus infection.

I venture to suggest that the untangling of this dilemma may well depend on the establishment of knowledge regarding the lesions all three agents induce in man. It is doubtless true that there are relatively few opportunities to examine the tissues of what seem characteristically to be self-limited and benign virus diseases, which, it seems to me, makes it all the more important to examine those we can. I am reminded of the radical change in our conception of catarrhal jaundice that followed Eppinger's chance observation during World War I and the comprehensive studies of World War II.

Cocksackie virus infection has frequently been associated, in our experience, with aseptic meningitis. It should also be noted that such viruses have been, on a number of occasions, isolated from patients with symptoms of myelo-radiculitis or the Guillain-Barré syndrome. This was initially reported by Rhodes (31) and has since been noted by Lépine (32). I doubt that this question may be satisfactorily settled by the isolation of virus or proof of an antibody response. But an association of virus and lesion might be decisive. All of which, I suspect, would amuse William Welch who would be tempted to note that at least one aspect of the infectious diseases has changed very little.

I come now to the second topic for discussion, the ecology of the Cocksackie viruses, their place in our parasitic environment. We have seen that they may occur in association with poliomyelitis virus and that their habits are similar. Is this perhaps of some special importance? It is, I believe, commendable that bacteriologists have become interested in the broader aspects of the little parasites; it is one of the most significant developments since Welch. Yellow fever taught the importance of natural reservoirs of infection of which human epidemics are but a deviation. We have become alert to the elegant adjustments between parasites and their hosts. Our knowledge of antagonisms between bacteria has provided us with the antibiotics. Is there, perhaps, something comparable involved in poliomyelitis? It is a puzzling question but with John Hunter (33) we may say: "I love to be puzzled for then I am sure I shall learn something valuable."

We know that under certain circumstances virus infections interfere with one

another and it is reported that they may enhance one another. The typical experiment, however, is one in which animals infected with one virus are temporarily refractory to infection with another. Interference may also occur between some bacterial and viral infections. The antagonism between vaccinia and whooping cough was put to practical use by Thomas Archer who was the first physician trained in North America. Archer discovered that if he vaccinated children in the early stages of whooping cough their whoops ceased about the time the vaccinia lesion became pustular (34). It was of considerable satisfaction to me some years ago, to show experimentally that this early report of interference could be duplicated in the laboratory (35). The interference phenomenon was rediscovered in the thirties and has been extensively investigated by means of the hemagglutination test. It was shown that certain viruses pre-empt cell receptors and thus prevent the union of other viruses with the same cells (36). I suspect that interferences in the living animal at times require other mechanisms as well as that of cell receptors, for the phenomenon is often quite complicated. In any case, it seems to be a significant natural phenomenon and, if you allow, I would like to quote a second time from Jacob Henle's *On Miasmata and Contagia*, "... almost every other disease is a preservative against the ruling epidemic."

We have known for 15 years that experimental poliomyelitis is modified by intercurrent infection with the virus of lymphocytic choriomeningitis (37). Recently we learned that Group-B Cocksackie virus also prevents or delays paralysis in mice inoculated with the Lansing strain of poliomyelitis virus (38). This is not a matter of cross immunity. It is only during the height of the Cocksackie virus infection that the mice are refractory to poliomyelitis. The experiments are similar to those in which lymphocytic choriomeningitis virus was used in time relationships, degree of protection, and the mutual effect the two viruses have on one another. In the original experiments the infectivity titers of both agents were depressed and it may be that the more perfect the interference the more difficult to demonstrate the presence of either.

Does anything of the kind occur in nature? We do not know. There would seem to be three methods of inquiry. The first would be the experimental one which would require that children in the earliest stages of poliomyelitis be infected with a suitable strain of Cocksackie virus and the outcome compared with adequate controls. Secondly, we might search individual patients and try to determine whether those who recover favorably or unfavorably are or are not instances of dual infection. This has been uppermost in my mind for a number of years and we have found that, in our limited experience, there has been an inverse relationship between the frequency of paralysis and of Cocksackie virus infection by years. Doctor Rhodes and his associates in Toronto also have this possibility in mind and Doctor Syverton, in Minneapolis, is currently testing the theory. There are, unfortunately, great difficulties for it would be desirable to measure infection and humoral response to both Cocksackie and poliomyelitis viruses and if an interference did occur it would of itself make this task more awkward and the results less certain.

The third approach would be an epidemiologic one. The 1948 Connecticut

epidemic of poliomyelitis, for example, was proven to be mixed. We know that a Group-B strain was present and that it is a strain capable of influencing the course of experimental poliomyelitis. From what we know of the Cocksackie diseases we may assume that infection was rather frequent throughout much of the state. The incidence of poliomyelitis was low. Unfortunately the frequency of paralytic cases, the only satisfactory measure of the prevalence of poliomyelitis, does not appear in the official records but it may be significant that no deaths were ascribed to poliomyelitis in Connecticut that year (fig. 2).

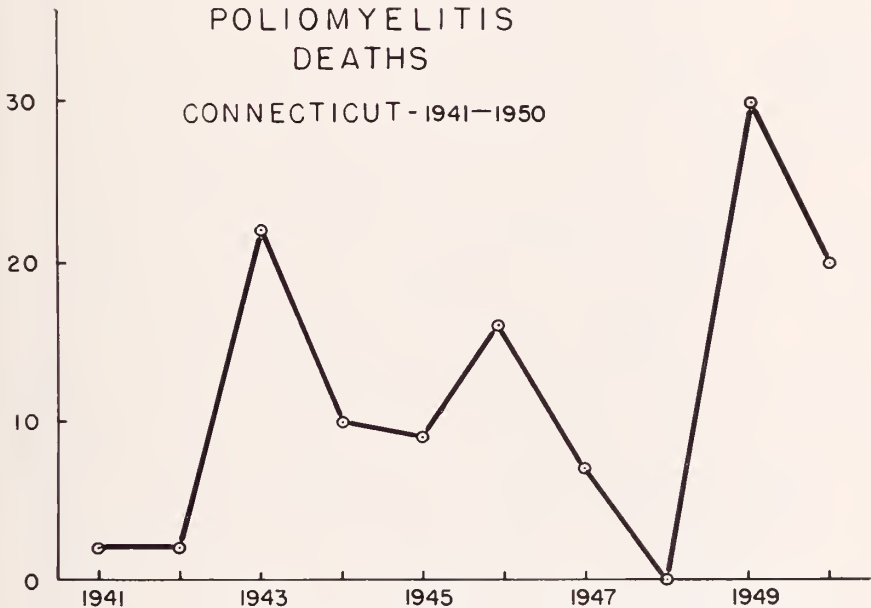


FIG. 2. Poliomyelitis deaths, Connecticut, 1941-1950

The largest known epidemic of pleurodynia occurred in Sweden in 1931 when 12,000 cases are estimated to have occurred during the late summer (39). Professor Kling told me of that epidemic and has since supplied the Swedish poliomyelitis records. I was greatly interested to note that the number of cases of paralytic poliomyelitis and of poliomyelitis deaths in 1931 were the least for the 20-year period covered by the records (fig. 3). This is itself a statistically significant deviation. Huss's report of the Bornholm epidemic includes a map indicating the distribution of the cases (39) (fig. 4). We have undertaken to determine whether the provinces in which Bornholm disease had been prevalent showed more or less poliomyelitis than would be expected by comparison with the years 1930 and 1932. The proportion of the poliomyelitis in all of Sweden represented by each province was calculated and the significance of the variations determined by means of four-fold tables. Bornholm disease was shown in Huss's map to have occurred in 10 of the 25 provinces; in 5 the records are ambiguous. The full weight of the epidemic was felt in the southern coastal provinces. In 4 of these

paralytic poliomyelitis did not occur at all. In each of the 6 provinces poliomyelitis was relatively infrequent in terms of 1930 and 1932. The 6 provinces reported 25 cases in 1930, 3 in 1931, and 191 in 1932. The reduction is significant, by mathematical standards, in 3 of the 6 provinces.

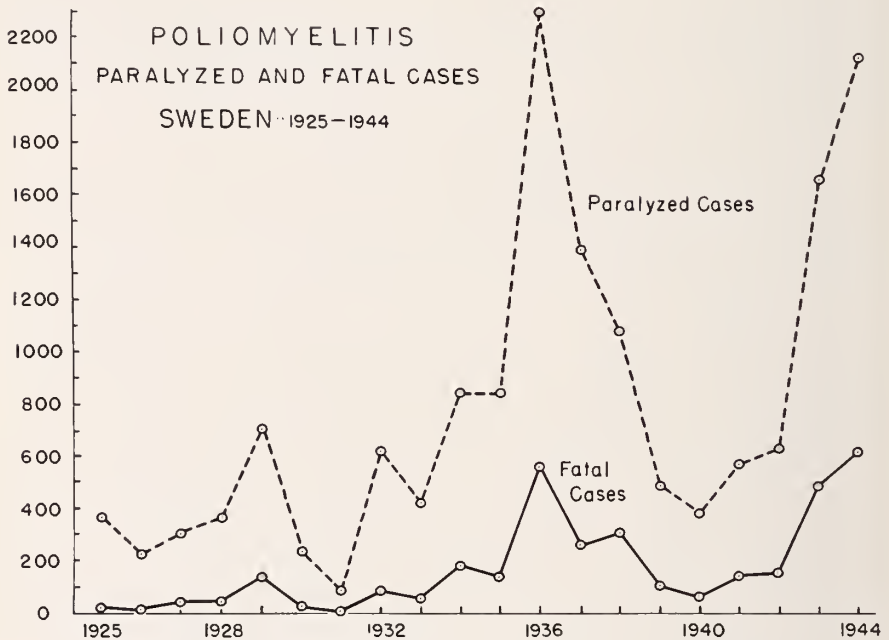


FIG. 3. Poliomyelitis, paralyzed and fatal cases. Sweden, 1925-1944

On the other hand, poliomyelitis was unusually prevalent in Bohus, on the western coast. Huss believed the epidemic had been introduced into Sweden by the crew of two warships that had docked at Marstrand, just north of Göteborg, in June. His records do not tell us when the Bornholm and poliomyelitis epidemics occurred in Bohus but he does say that the peak of the Bornholm epidemic on the southeastern coast was reached in August and September. And he noted that the city of Göteborg, which represents 70 per cent of the population of Bohus, was spared. Thus the increase in poliomyelitis in Bohus despite the prevalence of Bornholm disease may have been due to the fact that the two epidemics were dissociated in time or place. Unfortunately I am unable to verify either.

The province adjoining Bohus on the east had very little poliomyelitis and Huss's map does not indicate that Bornholm disease was present. These two provinces must therefore be considered as evidence against an interference. It may be noted, however, that poliomyelitis was disproportionately prevalent in two provinces in which Bornholm disease did not occur. I have arranged the significant results in a four-fold table (table 1). Of the 7 provinces in which the



FIG. 4. Epidemic myalgia in Sweden. (Reproduced from: Huss, Ragnar, La myalgie épidémique en Suède. Bull. Office Internat. d'Hyg. Pub., 1934, 26, p. 1085.)

variation was statistically significant, 5 may be said to favor the theory of an interference. This is hardly conclusive but is perhaps of some interest.

TABLE 1
Paralytic Poliomyelitis and Bornholm Disease
Sweden—1931

		Bornholm Disease	
		Prevalent	Absent
Poliomyelitis	Increased	0.0006	0.005 0.028
	Reduced	0.007	0.006
		0.017 0.029	

Discrepancy in terms of χ^2 between observed and expected prevalence of poliomyelitis in seven provinces.

If further observation indicates that these two diseases do inhibit each other, we would need to consider two possibilities. If dual infection in man behaves as it does in mice, we could expect that the incidence and severity of both diseases would be diminished. If dual infections were common, the poliomyelitis epidemic would then be unusually mild. This may have happened in Connecticut during 1948 and in Sweden in 1931. We should also expect that the isolation of both viruses might be unusually difficult and the number of isolations reduced. Of course the same effect would be simulated by concurrent epidemics involving different individuals, in which case the relative frequency of paralysis would be reduced through dilution of the whole by cases of the less severe disease.

There is another possibility. It has been shown that rat fleas, which are common vectors of plague, may be simultaneously infected with *Salmonella typhi-murium* and *Pasteurella pestis*. They are then poor transmitting agents of plague; they are incapable of propagating an epizootic and probably cannot keep the disease alive in enzootic form except under most favorable circumstances (40). It may therefore be that one of the limiting ecologic factors in plague is interference between a common rat *Salmonella* and *P. pestis* in the vector. In the case of a human disease that is transmitted directly, a comparable mechanism would also reduce infectivity and rate of dissemination. The incidence of disease would be diminished. We know of no vector of poliomyelitis. Infection is believed to be transmitted from man to man. But obviously the same mechanism would under such circumstances also lead to a suppression of the spread of infection. I fear it would be still more difficult of proof and that in any case I am guilty of "hanging heavy weights to slender wires." Nevertheless, it would seem to me to be unforgivable, having discovered that poliomyelitis has a close companion, a cousin or perhaps a brother, in the Coxsackie viruses, that we did not search the relationship for whatever significance it may have, for in all truth we so poorly understand it.

Tonight, as we cherish Welch's memory, we might perhaps all ask ourselves what he would have done.

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ARTERIOSCLEROSIS AND DIABETES

ERNST P. BOAS, M.D.

The frequent association of diabetes and arteriosclerosis has long been a matter of common knowledge, and is well documented. It is generally assumed that diabetes, in some occult manner, favors or accelerates the development of arteriosclerosis, but there have been some dissenting voices. The view defended by Enklewitz (1) and others that diabetes is a manifestation of degenerative vascular disease, is not supported by necropsy studies. In 1941 Dry and Hines (2) concluded, from a study of peripheral vascular disease in diabetics, that the concomitance of the two conditions is due to an inherent abiotrophy affecting both insulin producing and vascular systems. Levine (3) suggested that diabetes may not be the cause of coronary artery disease, but that diabetes may merely indicate a vascular vulnerability. Most recently Dolger (4) has emphasized that cardiovascular disease is not a complication of diabetes, but an integral component of the disease. He points out that "diabetic complications" are often fully developed by the time the diagnosis of diabetes is made; that they may even precede the appearance of hyperglycemia and glycosuria. He believes that arteriosclerosis, hypertension and diabetes may have a common origin which induces insulin insufficiency only incidentally and only in susceptible individuals.

The link between diabetes and arteriosclerosis is manifested most strikingly in the young. Joslin found evidence of vascular damage in 70 per cent of 250 juvenile diabetic patients after 20 years' treatment. Wilson, Root and Marble (5), from a study of 247 patients whose diabetes had begun between the ages of $1\frac{1}{2}$ and 30 years and had lasted for from 10 to 34 years, conclude that calcification of the arteries, retinitis and albuminuria occur more often among those whose diabetes is poorly controlled. Patients with good control of their diabetes did not show advanced arterial calcification, pronounced retinitis, nor diabetic nephropathy. However, minimal calcification was little affected by the degree of control of the diabetes. Actually only 37 of all of their cases had had excellent or good control of their diabetes. The authors do not distinguish between medial and intimal arterial calcification. Spoont and his associates (6) also report a higher incidence of retinopathy among poorly controlled diabetics. However, Dolger (7) reported that after 25 years' observation not one of 200 diabetic patients escaped retinal hemorrhage, regardless of the age of onset, the severity of the diabetes or the method of treatment. Bell (8) from a study of 1,025 autopsied cases concluded that the vascular lesions in diabetics are independent of the severity of the diabetic state. The duration of the diabetes seemed to influence the development of arteriosclerosis of those who died before age 60 but had little effect in those who died at older ages. However, the number of cases in his younger age groups are so few that the conclusions are not quite convincing. There were 55 persons who had survived their diabetes over 20 years, and of these 17 showed only minimal arteriosclerosis.

Unravelling of the relationship between diabetes and arteriosclerosis in the

older age groups is still more difficult because of the great frequency of arteriosclerosis in persons over age 50. Most of the pertinent literature, which concerns itself largely with necropsy studies, has been summarized by Liebow and Hellerstein (9). All the studies stress the high incidence of coronary artery disease in diabetics, as well as the fact that women diabetics are affected by arteriosclerosis as frequently as are men. Root (10) and his associates, for instance, found that among 316 diabetics over age 40 who were studied at necropsy 38.2 per cent of the men and 32.2 per cent of the women had had coronary artery occlusion; whereas among a much larger number of non-diabetics only 9.9 per cent of the men and 4.9 per cent of the women had had coronary artery occlusion. Dry and Hines, taking peripheral arterial disease as a measure of arteriosclerosis found peripheral arteriosclerosis much more common and more severe among diabetics, and noted that on the average it occurred a decade earlier in diabetic men, and 20 years earlier in diabetic women. Stearns (11), employing an injection technique, found coronary artery disease in three quarters of all diabetics; in diabetic women over age 40 the incidence of arteriosclerosis was as great as it was in men. The greater incidence of coronary artery sclerosis in diabetic women has also been demonstrated by Ackerman (12) and by Clawson and Bell (13).

Because he finds no increase of what he calls hyperplastic arteriosclerosis of the pulmonary artery in diabetics, Moscheowitz (14) concludes that diabetes does not cause arteriosclerosis. Hart and Lisa (15) made a careful necropsy study of 45 diabetics who had had their disease for 5 years or more. Seven patients had no evidence of arteriosclerosis, and 4 had only moderate arteriosclerosis. Of these 11 patients, 5 had had their diabetes for 5 years, 2 for 8 years, and 4 patients had had diabetes for 10, 15, 20 and 28 years respectively.

The great frequency of arteriosclerosis in diabetics, its high incidence in diabetic women, its almost universal development in young diabetics after a period of 20 to 25 years suggest, at first blush, that the diabetes is the cause of the arterial disease. However, the facts that the time of onset and the intensity of development of the arteriosclerosis is little affected by the treatment of the individual case; that it may develop in the patient whose glucose metabolism has remained under ideal control, as well as in the patient who has neglected himself; and the observation that many persons with long standing diabetes may at necropsy show only minimal arteriosclerosis throw doubt on such an etiological connection.

In an attempt to gain a better insight into the relationship between diabetes and arteriosclerosis I have studied 750 cases from my office files. The clinical material is to a certain extent selected because the majority of patients consult me for an opinion on their cardiovascular status. The first 500 charts bearing the diagnosis of diabetes mellitus were culled seriatim from the alphabetical name file. Similarly 250 consecutive charts with the diagnosis of coronary artery sclerosis without diabetes were selected from the same file.

The cases were grouped into four classes: A—patients in whom evidence of arteriosclerosis developed after the onset of diabetes, B—patients in whom evidence of arteriosclerosis developed before the onset of diabetes, S—patients in

whom the diagnoses of arteriosclerosis and diabetes were made simultaneously, O—patients who had only diabetes and no evidence of arteriosclerosis, C—patients who had only coronary artery sclerosis and no evidence of diabetes.

Criteria for the diagnosis of arteriosclerosis were: unequivocal evidence of coronary artery sclerosis as manifested by electrocardiographic changes or clas-

TABLE I

CLASS	CASES		AVERAGE AGE AT ONSET						AVERAGE INTERVAL
	Number	Per cent	Diabetes			Arteriosclerosis			
			Age	S.D.	P.E.	Age	S.D.	P.E.	
Males									
A	145	50.2	48.3	10.4	.585	56.2	7.6	.425	<i>years</i> 7.9
B	56	19.4	56.1	6.7	.604	51.2	8.1	.727	4.9
S	48	16.6	55.1	8.4	.821	55.1	8.4	.821	
O	40	13.8	51.2	7.8	.835				5.2*
Total	289								
C	204					52.7	8.4	.395	
Females									
A	99	46.9	47.5	7.1	.48	56.7	9.6	.653	9.2
B	22	10.4	56.4	7.6	1.09	53.5	7.9	1.137	2.9
S	15	7.1	56.4	8.5	1.47	56.4	8.5	1.47	
O	75	35.5	49.4	8.2	.635				8.2*
Total	211								
C	46					54.1	7.3	.723	

* Duration of diabetes.

A—Onset of arteriosclerosis after onset of diabetes.

B—Onset of arteriosclerosis before onset of diabetes.

S—Simultaneous onset of arteriosclerosis and diabetes.

O—Diabetes with no manifest arteriosclerosis.

C—Coronary artery sclerosis with no manifest diabetes.

S.D.—standard deviation. P.E.—probable error.

sical anginal pain, or impairment of the arterial circulation in the lower extremities. A study of the eyegrounds was not undertaken.

Data such as these, of course, do not reflect the correct age of onset either of diabetes or of arteriosclerosis. Both conditions may be present for years before becoming clinically manifest. The onset of diabetes could theoretically be determined more precisely by doing repeated sugar tolerance tests on patients with clinical signs of arteriosclerosis. The data of this study record the incidence of clinically manifest diabetes and arteriosclerosis in persons over age 40. Tables I and II summarize the findings.

The figures cited are in general agreement with those of other observers. Root and Graybiel (16) in 1931 studied 210 patients with diabetes and angina pectoris. The average age of onset of diabetes was 51 years, of angina pectoris 60 years. In 9 patients the anginal syndrome preceded the onset of diabetes, in 13 it appeared simultaneously with evidences of diabetes. Dr. Harry Gold has kindly permitted me to use the following figures prepared by Miss Claire Lingg from a

TABLE II

	MALES		FEMALES		RATIO MALE:FEMALES
	No.	%	No.	%	
A	145	59.4	99	40.6	1.5:1
B	56	71.8	22	28.2	2.5:1
S	48	76.2	15	23.8	3.2:1
O	40	34.8	75	65.2	0.5:1
Total	289	59.8	211	40.2	1.4:1
Arteriosclerosis only	204	82	46	18	4.4:1

study of arteriosclerotic heart disease that he is making under the auspices of the New York Heart Association:

PATIENTS WITH CORONARY ARTERY DISEASE	MALES		FEMALES	
	Number of cases	Mean age at onset of heart disease	Number of cases	Mean age at onset of heart disease
Non-diabetics	636	56.35 \pm .38	257	54.05 \pm .58
Diabetics	105	56.05 \pm .82	73	54.3 \pm 1.07

Master (17) reported on 500 patients with myocardial infarction and found the average age of onset of the initial attack to be 54.7 years for men and 56 years for women. He does not indicate how long the heart disease had existed before the initial myocardial infarction.

In 19.4 per cent of the men, diabetes developed on the average 4.9 years *after* the onset of signs of arteriosclerosis, and in 10.4 per cent of the women, diabetes appeared on the average 2.9 years *after* the recognition of arteriosclerosis. In 16.6 per cent of the men, and in 7.1 per cent of the women diabetes and arteriosclerosis were discovered simultaneously (table I). Several authors (2, 4, 12) have observed evidence of arterial disease in the leg arteries, the coronary arteries or the arteries of the eyegrounds before the appearance of glycosuria or hyperglycemia. In these cases, certainly, diabetes cannot be regarded as the cause of the arteriosclerosis. It may be that in these patients there is no causal relationship between the two diseases but that these older arteriosclerotics coincidentally have developed diabetes; or there may be a common underlying cause.

The age of onset of manifest arteriosclerosis is unaffected by the antecedent

diabetes, which in the males has existed 7.9 years, and in the females 9.2 years, on the average. Indeed, these patients with antecedent diabetes, both men and women, are older when they develop manifest arteriosclerosis than are those who develop their arterial disease first. The difference between the mean ages of the two series is significant. For males this difference is 6 times, for females, 2.5 times the standard error of the difference between the means. The average age of onset of arteriosclerosis in patients whose arteriosclerosis appears before diabetes corresponds closely to the average age of onset of arteriosclerosis in non-diabetics.

It appears that in this series of cases, diabetes has not accelerated the development of arteriosclerosis; the two conditions seem to develop independently. Clawson and Bell (13) conclude from their study of 50,775 necropsied cases that fatal coronary disease is twice as frequent in diabetic as in non-diabetic males, and three times as frequent in diabetic as in non-diabetic females, and that therefore diabetes accelerates coronary atherosclerosis. I have calculated the average ages at death from coronary disease of the patients over age 40 recorded in their table with the following results:

	AGE AT DEATH FROM FATAL KORONARY DISEASE	
	Males	Females
Non-diabetics	62.6	69.5
Diabetics	65.7	66.9

Levine (3) has pointed out that the average age at death of patients with angina pectoris and diabetes is essentially the same as for those without diabetes. These data give no support to the thesis that diabetes accelerates the progress of arteriosclerosis.

In the absence of diabetes, arteriosclerosis of the coronary arteries occurs about four times as frequently in males as in females. In my series of arteriosclerotics without diabetes the ratio of men to women is 4.4 to 1. In the diabetic group the ratio is 1.4 to 1 for the whole series, 1.5 to 1 for those developing diabetes first, 2.5 to 1 and 3.2 to 1 for those developing arteriosclerosis first or simultaneously, respectively, and 0.5 to 1 for those who have not developed arteriosclerosis (table II). Among all diabetics with manifestations of arteriosclerosis the proportion of men to women is 1.9 to 1. These figures confirm the observations of others that arteriosclerosis is more common among diabetic than among non-diabetic women. But, as table II shows, the predilection of arteriosclerosis for males persists among diabetics, too.

Diabetes develops at earlier ages in those patients of my series in whom the diabetes antedates the arteriosclerosis, or in whom there is no evident arteriosclerosis. It may be that we are dealing with different forms of diabetes.

Hypertension, too, is very common in diabetics (9). The published statistics are not very comprehensive, but they suggest that approximately one-half of all diabetics over age 50 have hypertension. In John's (18) series 26 per cent of

548 men and 50 per cent of 533 women over age 40 had systolic blood pressures over 150 mm. mercury. Martenson (19) found blood pressures over 150/90 in 48 per cent of 111 men and in 65 per cent of 110 women who had had diabetes at least 15 years. In Bell's series (8) at least 54 per cent of men and 67 per cent of women had systolic pressures over 150 mm. mercury.

In table III is recorded the incidence of hypertension in the present series. A systolic pressure of 150 mm. mercury and a diastolic reading of 90 mm. mercury were arbitrarily chosen as the upper limits of normal. Blood pressures were taken by myself with a mercury manometer with the patient in a recumbent position. In most instances several successive readings were taken, and the final lowest reading was recorded (20). Master, Dublin and Marks (21) have

TABLE III

	PER CENT OF PATIENTS WITH			AVERAGE AGE AT OBSERVATION	AVERAGE DURATION DIABETES
	Hypertension	Cardiac Enlargement	Albuminuria		
Male					
					<i>years</i>
A	31.9	54.4	31.3	59.7	10.4
B	32.1	53.5	32.7	59.1	3.0
S	35.4	55.5	29.8	57.8	2.7
O	37.5	35.0	30.0	56.4	5.2
C	29.0				
Female					
A	72.8	74.4	39.0	59.5	12.0
B	81.8	81.8	54.5	59.8	3.4
S	60.0	66.6	33.3	57.8	1.4
O	65.3	56.1	42.4	57.6	8.2
C	63.0				

recently presented data to prove that the normal blood pressure of older persons may have a much higher range than has been assumed. Their clinical material consists of applicants for employment in industrial plants and army airfields whose blood pressure was measured under unstandardized conditions by many different persons. The authors do not state whether the readings were made with the applicant in a sitting or lying position, nor what the attendant circumstances were, nor whether the blood pressure was measured by a physician or by a nurse or technician. The blood pressure is so variable that studies based on such uncontrolled readings have little general validity. In their study a blood pressure of 140 systolic and 90 diastolic or over was found in 40 per cent of men and women between the ages of 45 and 49, and in 60 per cent between the age of 60 and 64.

One third of the diabetic men and about 70 per cent of the diabetic women had blood pressures over 150 systolic and 90 diastolic (table III). Cardiac en-

largement as determined by fluoroscopy, was found in about one half of the men. Probably the more advanced degree of coronary arterial disease in the men contributed to the development of cardiac enlargement. In the women the frequency of cardiac enlargement paralleled that of hypertension. Many of these patients have been under observation for years and the blood pressure reading that is recorded in the table represents the reading at the last observation. It is apparent from the figures that neither the age of the patient nor the duration of the diabetes influenced the incidence of hypertension.

The incidence of hypertension in diabetic males is not significantly greater than among males with coronary sclerosis and without diabetes, and appears lower than that of the male population at large. Diabetic females, too, do not seem to have more hypertension than do women with coronary artery sclerosis alone, but the incidence of hypertension seems to be greater than among the female population at large.

COMMENT

Necropsy studies have demonstrated that arteriosclerosis is more common among diabetics than among non-diabetics, particularly in women. The present study of older diabetics has shown that in 36 per cent of males and in 17.5 per cent of females with both diseases the diabetes becomes manifest either after or simultaneously with the clinical appearance of arteriosclerosis. Preexistent diabetes does not accelerate the development of arteriosclerosis, indeed, the average age of onset of signs of arteriosclerosis is greater in patients who have had antecedent diabetes than in those who develop their diabetes subsequently, or those with coronary artery sclerosis who do not have diabetes. The two diseases seem to develop quite independently.

The ratio of men to women among diabetics with arteriosclerosis is 1.9 to 1, in contrast to a ratio of 4.4 to 1 that prevails among arteriosclerotics without diabetes. This confirms the well established fact that arteriosclerosis is much more common among diabetic than among non-diabetic women. However, the predilection of arteriosclerosis for males is apparent among all the diabetic groups in the present study.

Since diabetes does not accelerate the development of arteriosclerosis, but since arteriosclerosis occurs more commonly among diabetics than among non-diabetics there must be a common constitutional basis for both disorders. Since proportionally more diabetic women than men are affected by arteriosclerosis this constitutional tendency must be more potent or more widely distributed in women. Hypertension is twice as frequent among diabetic women as among diabetic men, and probably more common than in the female population at large. Possibly the link between diabetes and arteriosclerosis in women is hypertension; but this still leaves unexplained the great frequency of hypertension among diabetic women.

If it is true that arteriosclerosis and diabetes both arise as a result of a common constitutional disorder, studies of the familial incidence of both diseases should give a clue to this association. The only approach to such a study that I

have found is by Root and Graybiel (16) but they do not give sufficient details to permit a thorough evaluation of the significance of their findings. They report the family history of both diabetes and vascular disease in 210 diabetics with angina pectoris. They do not define what is included under vascular disease. The following tabulation summarizes the number of patients of their series who gave family histories of diabetes and vascular disease:

DIABETES WITHOUT VASCULAR DISEASE	DIABETES WITH VASCULAR DISEASE	VASCULAR DISEASE WITHOUT DIABETES	VASCULAR DISEASE TOTAL	DIABETES TOTAL
47	26	73	99	73

A comprehensive study of the familial incidence of diabetes, hypertension and arteriosclerosis may throw new light on the whole problem.

SUMMARY

A statistical study of 500 diabetics over age 40 indicates that although there is a common association of diabetes and arteriosclerosis, particularly evident in women, the presence of diabetes, even for many years, does not accelerate the progress of arteriosclerosis. Hypertension appears to be more common in diabetic women than in females in the general population. There is probably a constitutional hereditary basis for the association of these several diseases.

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JUDICIUM DIFFICILE. A LESSON IN PERSPECTIVE*

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We, in the United States, are often accused of overspecialization. And a specialist has, in a lighter moment, been defined as "one who knows more and more about less and less." Yet, it can be easily proven that the individual patient, suffering from some unusual condition, who finds himself in the hands of a specialist thoroughly acquainted with every aspect of his particular problem, stands a better chance of finding a solution to it than if he were obliged to be treated by the specialist's antithesis, namely a man who knows "less and less about more and more."

However, the isolated position of the specialist upon the outposts of knowledge in his own field, often forces him to make judgments unaided by books or rules or the comfort of consultation with some colleague. Years may pass before the results of such decisions can be evaluated, and it is rare for a clinician to have an opportunity to measure his wisdom against a control experiment.

The almost simultaneous appearance of two patients with almost exactly the same conditions, and their eventual treatment in two different ways, presented an opportunity for a clinical experiment, each case serving as a control for the other, which is rarely encountered and thus deserves recording.

Both patients were young men. L. S., trained as an accountant and working as assistant comptroller in a large retail business, was 28 years of age when first seen on March 9th, 1945. D. F., trained as an accountant and working as a cost analyst in a government department, was 29 years old at his first visit on December 26th, 1945. The first was left-handed and the second was right-handed, and while they proved to have tumors of cerebral hemispheres opposite from each other, a cynical fate had decreed that each one's tumor affected his dominant hemisphere. L. S., the left-hander, had his tumor in the right parietal lobe, and D. F., the right-hander's growth was in his left parietal lobe.

From this point on, to avoid confusion, it may be well to follow the course of events in each case separately.

Case 1: L. S. was the first of the two to consult our clinic. He came in March, 1945 to complain of two convulsive seizures occurring one, four months and the second, two days before his visit. For two weeks he had been having headaches. This was his simple story, to which his past and family history added nothing. He was happily married, had two children and, up to the present illness, considered himself in excellent health.

He was a fine, intelligent young man and although his tumor proved to be in the right, which was *his* dominant hemisphere, he showed no evidence of aphasia. Indeed, neurological examination revealed a remarkable paucity of positive signs. The only abnormality was bilateral early papilledema. The diagnosis and location of his tumor, however, was not difficult, because electroencephalographic studies revealed a sharply localized area of abnormal electrical activity confined to the right parietal region (fig. 1e), and roentgenograms of the skull showed an abnormal deposition of calcium deep in the right parietal region

* Delivered as the Chairman's opening address of the Medical Teaching Mission of the World Health Organization and the Unitarian Service Committee to Israel and Iran, at Tel Aviv, August 31, 1951.

such as one frequently sees in cases of the more benign gliomas, as, for example, astrocytoma or oligodendroglioma.

The difficulty in this case obviously was not in making the diagnosis but in deciding on the method of treatment. Some type of operation was necessary since the increased intracranial pressure, as indicated by headaches and papilledema, had to be relieved. The question was whether a) to attempt to remove the tumor, or b) to follow a more conservative course, namely produce a decompression and then try to retard the growth of the tumor by roentgen irradiation. In favor of the first were: 1) modern surgical technique makes the removal of such tumors quite feasible, 2) astrocytomas or oligodendrogliomas, when a sufficient amount of surrounding brain tissue is taken away, may at times be removed *in toto* without much risk of recurrence. Against this more radical undertaking was: 1) the certainty that a transcortical excision of the tumor would result in a contralateral loss of sensation and power that would, if not permanent, at best, last for a long time. 2) The tumor involving the dominant hemisphere might result in at least temporary aphasia. 3) Finally, in spite of risking paralysis and aphasia, the tumor might, in the course of time, recur anyway, since total removal of these tumors is the exception rather than the rule.

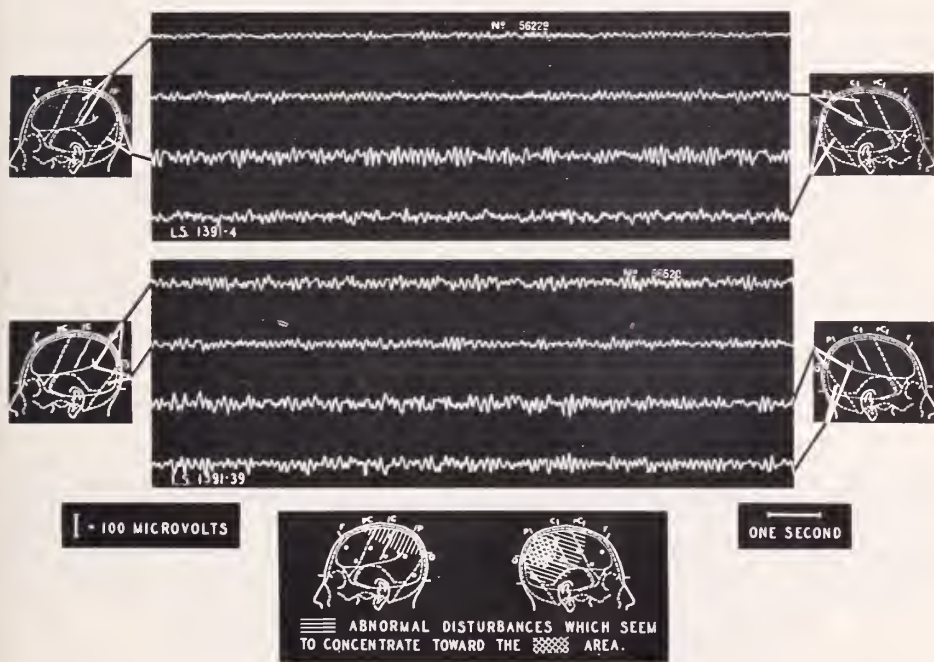


FIG. 1. Electroencephalogram in case 1

In view of the almost complete absence of abnormal signs, it was decided to pursue the more conservative course. On March 19, 1945, a decompression was carried out, and a course of roentgen irradiation was instituted. Phenobarbital was prescribed to control his seizures. Within a few weeks his primary complaint of headaches had disappeared and the patient returned to full-time employment.

For a period of three years he remained perfectly well except for one or two minor seizures when he neglected his medication. In June, 1948, he began to have occasional headaches and a period, lasting several days, when his left hand felt awkward and weak. He had a similar episode in August and a third one in October of 1948, and was readmitted to the hospital.

On admission, he showed a left upper homonymous quadrantanopsia, slight weakness and slight stereognostic disturbances in his left hand. But his decompression was rather tense and we believed that his period of grace had run out, and we offered him radical operative intervention.

At the patient's own request, however, further roentgen irradiation was instituted, and in the course of several weeks he felt so much better that he returned to work. His maturity in connection with his job had increased to the point that his firm sent him to California where he successfully opened a branch business. He remained well for an entire year, but then began to show increasing left-sided weakness and occasional groping for words.

On January 2, 1950, he was readmitted to the hospital where he was found to have left-sided paresis, left homonymous hemianopia and moderate anomia.

On the 5th of January, a gross total removal of his tumor was carried out and it proved, histologically, to be a piloid astrocytoma.

Immediately after the operation, he was completely aphasic and left hemiplegic. Fortunately he recovered quickly his speech mechanism and improvement in power in his left side began before he left the hospital.

By March the weakness was manifested only by a slight limp. The arm and hand were almost normal. Meanwhile, as a precaution, he had learnt to write with his right hand. When last seen in September, 1950, he considered himself essentially well.

Case 2: D. F. came to our attention in December, 1945, 9 months after we made the acquaintance of L. S. His history was of even briefer duration, namely 3 weeks, and consisted of headaches, vomiting and a ringing noise in his head. His past history included an attack of rheumatic fever in childhood, without cardiac complications, and a cerebral concussion two years before. He too was married and his wife was pregnant for the first time. D. F. was right-handed, but though he proved to have a tumor in the left cerebral hemisphere, he, too, showed no evidence of aphasia, nor indeed any other localizing signs except for absent right abdominal reflexes. His only significant positive sign was bilateral papilledema.

Electroencephalography revealed a sharply localized area of abnormal electrical activity in the left parietal region (fig. 2). Roentgen studies of the skull showed a moderate degree of atrophy of the sella turcica and an area of calcification deep in the left parietal region similar to that seen in the right parietal region of L. S.

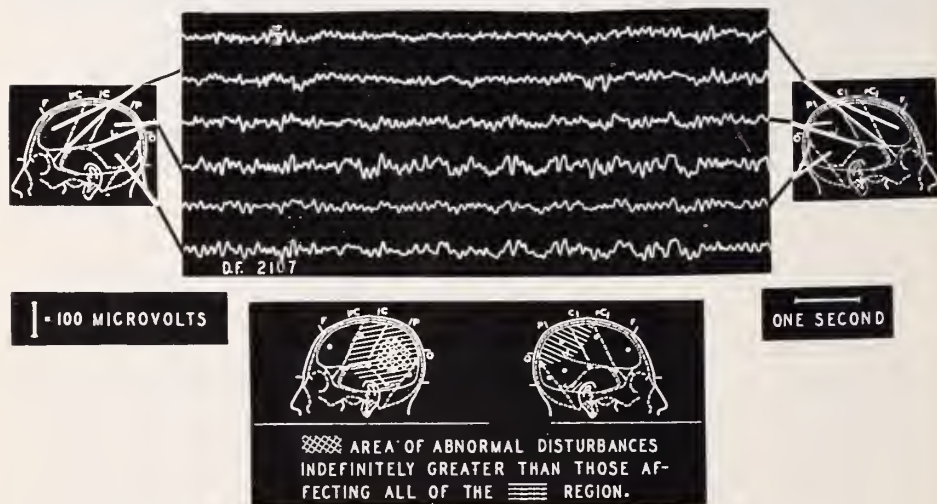


FIG. 2. Electroencephalogram in case 2

In the light of our experience with the first case, 9 months before, we unhesitatingly concluded to treat him the same way, and explained our plan, and the reasoning behind

it both to the patient and his family. They agreed to have a decompression done, and this was carried out on January 3rd, 1946, followed by a course of roentgen irradiation.

He was next seen on March 13th, 1946. His headaches, vomiting and papilledema had diminished and he was well in every other way but for slight weakness in his right hand. He was, however, working full time at his job. We felt that the situation was under control and advised him to continue with his work and to report periodically for reevaluation of his condition.

His family, however, was greatly perturbed by the knowledge that his brain still harbored a tumor, and sought advice at another clinic in another city. There, immediate operation was urged upon them, and on March 22nd, 1946, a gross total removal of the tumor was carried out. Unfortunately no histological description of the tumor was obtainable.

He was completely aphasic and right hemiplegic immediately after the operation. The aphasia began to improve shortly afterwards, but it was one and one-half years before he had a restoration of speech to a reasonably normal level. The paralysis has remained practically complete in the right upper extremity, but was partially restored in the lower one. By dint of admirable effort, he has learnt to write, feed and dress himself, and even to drive a car, using his left hand alone. It was two years before he could start working and when last seen in October, 1950, he was able to work only half days, because he became too fatigued both physically and mentally to continue after 3 or 4 hours.

DISCUSSION

The parallelism in these two cases ceased because D. F. was less fortunate in the results of the definitive operation than L. S., but it is this very divergent outcome from their operations that complicates our problem. Let us assume that in both cases, after the removal of the tumor, the patients—as was true with L. S.—had brief convalescences and were then restored to full usefulness. In the light of such a result, it would seem in retrospect that L. S. was kept in a state of uncertainty for a period of five years which might have been avoided by attacking his tumor definitively when he was first seen. On the other hand, let us assume that the result of his operation, as was true with D. F., would have been prolonged invalidism and probably permanent partial disability, then the delay of the final operation for five years during which, with minor discomforts, he was able to work full-time, progress in his job and lay by some savings before he faced permanent partial disability, would have been five years saved for him and his family.

What, then, have we learnt from these two very instructive cases? During the greater part of the four years after D. F.'s tumor had been removed and his usefulness had been largely curtailed, while L. S. with only a decompression was leading an essentially normal existence, the writer was convinced that the correct course was that followed with L. S. After the latter's tumor was removed and his recovery was so uncomplicated, my assurance began to fail me, and I felt considerable perturbation about having delayed the tumor removal for so long in his case.

What should one do under similar circumstances in the future?

Indeed, with the father of modern medicine, we may say

Life is short
The art long
Experiment perilous
Decision difficult.

PERINEPHRIC AND RENAL CORTICAL ABSCESS DUE TO COLON BACILLUS WITHOUT BACTERIURIA OR PYURIA

KERMIT E. OSSERMAN, M.D. AND H. EVANS LEITER, M.D.

Chronic perinephritic abscess has been notorious for its difficulty in diagnosis. This is due to the obscurity of symptoms and the frequent lack of findings in the urinary sediment, especially in those abscesses caused by staphylococci. Most writers distinguish between abscesses caused by staphylococci and those due to other pyogenic organisms. There are differences not only in bacteriology, but also in etiology as well as symptomatology.

The most common cause of a perinephritic abscess is a hematogenous localization of staphylococci in the renal cortex with resultant cortical abscess and subsequent involvement of the perinephric space. Several days or weeks after an almost forgotten superficial infection, the patient may become acutely ill with a chill, fever and lumbar pain or tenderness. The urine is generally free of organisms, pus or blood (Hinman (1), Le Comte (2), (3), and others). This finding of a negative urine has been the accepted teaching for many years. Thus, Hinman (1) states that staphylococcic cortical infections are hematogeneous in origin and "as a rule the pelvis is not involved and the urine is usually negative." Nesbit and Dick (4), however, in a careful survey of the urinary sediment of eighty cases of staphylococcal infection of the kidneys made the following observations: The cocci could be demonstrated in the stained centrifuged urinary sediment of all the cases during the early stages of the disease. The microorganisms disappeared from the urine of some cases after 48 to 72 hours, while in others the bacteria persisted for as long as 90 days. About 50 per cent of the cases failed to show any leukocytes in the urine at any time. In over one third of the patients, secondary invasion of the urine by colon bacilli took place. When this occurred, the bacteria tended to persist and pus cells always appeared in the urine.

Perirenal abscess due to the colon bacillus is rare (Hinman (1)). When it occurs, the chronic perinephritic lesion is generally obscured by the more obvious pathology in the urinary tract. The lesion in the kidney is either an active pyelonephritis or pyonephrosis due to obstruction, calculi or other foreign bodies such as drainage tubes. Direct invasion of the perinephric space by colon bacilli may also follow closed or operative trauma to the urinary tract, and, in rare cases, perforation of the intestinal tract. Except in this last instance, the urine almost invariably shows the presence of bacteria, pus and other formed elements.

Since the introduction of the various antibiotics, the ravages formerly seen in acute pyelonephritis due to the colon bacilli have largely disappeared (5). This is especially true in those cases which are not complicated by either foreign body or obstruction in the urinary tract. It is important to emphasize, however, that although the administration of antibiotics may lead to a disappearance of both the pyuria and bacilluria, on rare occasions the drugs are ineffective in preventing the formation of a cortical renal and perinephritic abscess.

Thus, one of the features of interest in the subsequent case history is the pres-

ence of a chronic perinephritic and cortical renal abscess due to the colon bacillus without any apparent evidence of abnormality in either the renal pelvis or within the urinary sediment. By way of emphasis and example, the following case history is recorded:

CASE REPORT

History:—F. L., a 67 year old white married female was admitted to the Mount Sinai Hospital on February 8, 1950, because of fever, pyuria, and left upper abdominal pain. Previous history consisted of a fracture of the neck of the left femur in November, 1948, and a mild hypertension which had become more marked in January, 1950, and required bed rest. Her present illness began four days prior to hospitalization with a sudden onset of left upper abdominal pain, a fever up to 104° F., and percussion tenderness in the left costo-vertebral area. Urinalysis at that time showed numerous pus cells and her white blood cell count was 30,000 per cu. mm. with 88 per cent polymorphonuclear cells. The treatment which was promptly instituted consisted of daily injections of 400,000 units of penicillin and 2 grams of aureomycin in divided oral doses. Because of a persistence of fever and pain, despite the above therapy, hospitalization was deemed indicated for further study and therapy.

Examination:—The patient was an acutely ill, obese female with a fever of 102° F. General physical examination revealed no significant abnormalities except for distinct left costovertebral shock tenderness.

Course:—Penicillin therapy was stopped because of the onset of a rash. In addition to the same dosage of aureomycin, 3 grams of gantrisin were given daily in divided doses. Excretory urography revealed some calcification in the splenic area, but no evidences of radio-opaque urinary calculi were seen. This right renal pelvis was normal. The left renal pelvis was also normal, but it was noted that the lower pole of the left kidney was at a slightly lower level than that of the right kidney. The psoas margins were distinct, and there was no evidence of abnormal spinal curvature. The spine showed a mild degree of osteoporosis and osteoarthritis.

Cystoscopic examination revealed a normal bladder. Indigo-Carmine given intravenously appeared in strong concentration from both ureter orifices within a few minutes. A left retrograde pyelogram failed to show any abnormality. A culture of the catheterized bladder urine was sterile, and pyuria was absent.

Her symptoms and signs subsided very rapidly so that she was permitted to leave the hospital on February 12, 1950.

She felt well for several weeks but then again developed pain in the left upper abdomen. Re-examination in the early part of April, 1950, disclosed the following: There was a vague resistance in the left upper abdomen; a catheterized urine specimen was free of pus and sterile on culture; intravenous pyelography showed a normal kidney on both sides, but the spleen appeared enlarged. Because of the latter finding hematologic studies were done and were reported as follows:

Hemoglobin.....	18.0 Gm.
Red Blood Cells.....	6,140,000 per cu. mm.
White Blood Cells.....	20,500 per cu. mm.
Blood Platelets.....	490,000 per cu. mm.
Reticulocytes.....	.5%
Nonsegmented Neutrophiles.....	9%
Segmented Neutrophiles.....	67%
Lymphocytes.....	16%
Monocytes.....	5%
Eosinophiles.....	2%
Myelocytes.....	1%
Hematocrit.....	60

Bone marrow aspiration revealed a very cellular marrow with a total nucleated cell count of 60,000 per cu. mm. and 66 megakaryocytes per cu. mm. The differential bone marrow cell count was normal. A diagnosis of Polycythemia Vera was made.

Blood chemistries at the time revealed:

Uric acid.....	3.1 mg. %
Alkaline Phosphatase.....	10.1 King-Armstrong units
Total Protein.....	8.3 Gm. %
Icterus Index.....	4 units
Sedimentation Rate (Westergren).....	5 millimeters in one hour
Cholesterol Cephalin Flocculation.....	{ 24 hours—negative 48 hours—negative

The patient was treated by multiple phlebotomies during the succeeding two weeks without any notable improvement in the blood picture. Because of a persistence of symptoms, a total of 3 millieuries of radioactive phosphorus (P. 32) were administered in the next few weeks. The spleen remained enlarged and tender and the patient ran an intermittent fever to 102° F. By July, 1950, the hematocrit had fallen to 40; the hemoglobin was 12.1 grams; and the red blood cells were 4,520,000 per cu. mm.

Although the hematologic picture was improved, a low grade fever persisted, and there was a weight loss of 20 pounds. It was at first postulated that the pain remaining in the upper left quadrant and the fever might be due to a splenic infarct, but because of the elevated sedimentation rate of 35 mm., and the loss of weight, it was deemed advisable to re-study the entire problem, bearing in mind the possibility of a hidden neoplasm. Accordingly, roentgen studies were made of the gastrointestinal tract, colon, kidneys, and gallbladder. These failed to disclose any abnormality. The spleen was only slightly enlarged, the lower border extending just below the costal margin. The possibility of a tumor in the left upper quadrant was then considered. On abdominal examination the splenic edge could just be felt, and there was a sense of an indefinite mass in the upper left quadrant with some slight but deep tenderness. (There still remained tenderness in the left costovertebral region.) The patient was readmitted to the hospital on August 15, 1950, in order to perform a perinephric insufflation. The patient was prepared for this procedure, and after inserting the needle into the perinephric space, thick, creamy pus was aspirated through the needle. This pus revealed on culture a mucoid *B. Coli* which was four times as resistant as the standard organism to chloromycetin.

Further laboratory work-up revealed a blood alkaline phosphatase of 18 K.A. units; a blood uric acid of 9 milligrams per cent; hematocrit 38.5; erythrocyte sedimentation rate 58 mm. A left retrograde pyelogram, which was performed immediately after aspirating pus, showed evidences of distortion of the upper calyces.

Operative intervention, which was carried out through a left lumbar incision, exposed a cortical renal and perinephric abscess on the left side. Drainage of the abscess was followed by an uneventful recovery. The pathological report of tissue removed from the abscess areas showed "fragments of fibrous and granulation tissue of acute non-specific purulent inflammation."

The patient was discharged on the fourteenth post-operative day and has continued to be in good health. When last seen in March, 1951, she had regained 10 pounds in weight, felt well, and had no recurrence of left sided abdominal pain.

CONCLUSIONS

Emphasis should be placed on the occasions when antibiotics may obscure underlying renal pathology. These newer drugs have been extremely valuable in the rapidity and effectiveness with which they have eliminated urinary tract infections (5). There have been examples of infections in other parts of the body

where antibiotic agents have masked existent pathology. Such a note of warning was sounded by Garlock (6) on the use of penicillin in surgical infections.

We noted a disappearance of fever, pyuria and bacilluria in our case as a result of drug therapy. It would seem, however, that the failure of the medication to eliminate one focus of infection in the renal cortex undoubtedly led to the development of a cortical renal and perinephritic abscess. It is only by this mode of reasoning that one can explain the unusual combination of a perirenal abscess due to colon bacteria without bacilluria or pyuria.

As already stated, the diagnosis of chronic perinephritic abscess may be very taxing, and was rendered much more difficult in our case by the concomitant presence of a splenomegaly due to Polycythemia Vera, with the abscess located on the left side.

SUMMARY

A discussion of some features of difference between staphylococic and other pyogenic infections of the perirenal space were reviewed. It was noted that renal cortical and perinephric abscess due to *B. Coli* without pyuria and bacilluria is a rare occurrence. The possibility that antibiotic drugs may mask an underlying inflammatory pathology was emphasized. Lastly, a clinical history was recorded which exemplified the above factors.

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SPONTANEOUS RUPTURE OF NORMAL GALL BLADDER DUE TO BILIARY TRACT OBSTRUCTION*

DR. ALVIN J. KAHN

The occurrence of a spontaneous rupture of a normal gall bladder is so unusual that the report of such a case is warranted. A review of the available literature revealed only two previous instances of such perforation due to back pressure in the biliary tract from obstruction caused by a carcinoma of the head of the pancreas. One case was reported by Olmer and Aubanel (1) of Marseilles, the other by Lachman (2).

CASE REPORT

History: A 77 year old white widowed housewife, gravida 6, para 6, entered the hospital on September 28, 1951 because of jaundice of two weeks duration. A year previously, she began having intermittent subcostal girdling pain. The abdominal pain would last several hours, occasionally radiating straight through to the back. In September of 1951 she was examined at another hospital and was told that she had gall bladder disease. There had been a weight loss of 45 pounds in one year. During the past three months, these pains became worse and frequent eructation was noted. In July she began having 4-5 watery, white or brown bowel movements daily with accompanying marked weakness. Approximately two weeks prior to admission to this hospital, jaundice developed and clay colored stools and dark urine were observed. Exploratory laparotomy was recommended after a complete gastro-intestinal x-ray study had failed to reveal the cause of the complaints.

Examination: Blood pressure 112 systolic and 50 diastolic. Pulse, 86. Temperature, 98.6° F. Respiration, 20. The patient was a thin, emaciated, jaundiced, white female, appearing her given 77 years. She was alert, cooperative, and in no distress. The conjunctivae and sclerae were icteric. There was marked distention of the lower abdomen, no pain, tenderness, or rigidity. A questionable mass was palpable in the right upper quadrant, thought to be an enlarged gall bladder.

Impression: Obstructive jaundice due to carcinoma of the pancreas.

Laboratory data: Urine: specific gravity, 1.032, bile, 1 plus, albumin trace, sugar negative; 6-8 white blood cells; occasional red blood cells and uric acid crystal, urobilinogen, 1:20. Prothrombin time: 9/28/51—patient 12/seconds, control 12/seconds. 9/30—patient 13.5/seconds, control 12/seconds. 10/1—patient 12.5 seconds, control 12.5/seconds. Complete blood count: Hemoglobin 11.2 gm. per cent. White blood cells, 5,600; segmented, 65; nonsegmented, 2; lymphocytes, 28; mononuclear, 3; basophiles, 1, eosinophiles, 1.

September 28—Icteric index, 20; Bilirubin, 1.3 mg. per cent; VandenBergh (direct), delayed positive. Cephalin flocculation, 1 plus. 10/1—icteric index, 50.

Course: On the evening of September 30, 1951, the patient complained of chest pain, nausea and cramping abdominal pain, sufficiently severe to cause her to cry. Her temperature was 101° F. There was tenderness of the right upper abdominal quadrant. An infusion of 1,000 cc. of 5% glucose was given. During the subsequent two days the temperature was 100° F. and the patient complained of nausea, generalized weakness, and had occasional vomiting. On October 3, 1951, the nausea and vomiting had disappeared. The patient felt and ate well. On the day of operation, it was thought that there was fluid in the abdomen.

Operation: (October 4, 1951—Dr. Garlock). Through an upper right rectus incision, the abdomen was opened and approximately 3,000 cc. of greenish, peritoneal fluid was evacuated. The omentum was stained dark green. The peritoneum and mesentery were not inflamed. The gall bladder appeared normal, though moderately distended. Approximately 3 cm. from the neck of the gall bladder and on its undersurface, was a 2 mm. perforation through which thick, dark, green bile was exuding into the free peritoneal cavity. A

* From the Surgical Service of Dr. John H. Garlock.

stony mass, the size of a lemon was palpated in the head of the pancreas and diagnosed as adenocarcinoma of the head of the pancreas. A cholecystogastrostomy was done. The patient was returned to her room in good condition.

After an uneventful course, she was discharged on the 12th post-operative day with primary wound healing.

DISCUSSION

Perforations of the gall bladder due to inflammatory disease are too well known to merit extended discussion here. The important feature in this case is that perforation occurred in a previously normal organ which became markedly distended as a result of obstruction in the distal biliary tree. The rarity of this complication is attested to by the paucity of reported cases.

It is interesting to speculate on the probable mechanism of perforation of a normal gall bladder in the presence of increased intrabiliary pressure. The explanation may well be connected with the presence of mucosal diverticula in the gall bladder wall, producing localized areas of thinning (3 and 4). Von Rokitsky (5) and Aschoff (6) were among the first to describe these tubular and racemose glands located usually near the neck of the organ and extending to the muscular wall, and often also into the muscle lacunae. These glandular structures, known as Aschoff-Rokitansky sinuses, Luschka's crypts, or diverticula, occur in 35 per cent of normal gall bladders (4 and 7). It is surmised that in the case reported here, dilatation of the gall bladder resulted in rupture of one of these areas of diminished resistance.

Of interest also in this particular case, is the relatively benign course in the presence of a diffuse biliary peritoneal insult. The rupture apparently took place on September 30th, and the ensuing mild acute symptoms subsided within three days. The sudden development of fluid in the peritoneal cavity at this time was the clue which could have permitted suspicion of the probable underlying mechanism.

SUMMARY

A patient with carcinoma of the head of the pancreas is reported in whom perforation of the dilated normal gall bladder occurred. The possibility is discussed that in the patient reported here, the perforation of the gall bladder was associated with a localized thinning of the wall at the site of abnormally large Aschoff-Rokitansky sinuses.

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ABSTRACTS

AUTHOR'S ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL, STAFF

Members of the hospital staff and the out patient department of the Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

Sjorgen's Syndrome. H. T. BEHRMAN. Arch. Dermat. & Syph., 61: 63, January, 1950.

This report is the first one in the American dermatologic literature of a case of Sjorgen's syndrome. This rare systemic disorder combines a group of functional disturbances affecting embryologic derivants of ectodermal and endodermal tissue. The cause is as yet unknown, but has been believed to be related to vitamin A and B deficiency as well as to disturbances in mineral metabolism and endocrine function. In view of these theoretic possibilities, the patient described in this report was admitted to the Mount Sinai Hospital, where extensive studies were performed in an attempt to elucidate fundamental causative factors. This discussion includes a review of pertinent facts relevant to etiology, symptomatology, pathology and therapy.

Recent Trends in Cesarean Section. R. G. DOUGLAS AND R. LANDESMAN. Am. J. Obst. & Gynec., 59: 96, January, 1950.

At the New York Lying In Hospital there has been a gradual increase in the incidence of cesarean section from 2% to 4%. The low flap transperitoneal section has replaced the classical and extraperitoneal techniques. The low flap operation is simpler to perform, is without adjacent structure injury, and is without protracted wound drainage. With the prophylactic use of modern surgical supportive therapy, including antibiotics, electrolyte and fluid balance, and intestinal intubation, the extraperitoneal section has not been indicated in recent years at this clinic. Our data clearly indicates that infection may be eliminated as a cause of mortality or as a serious complication when the low flap operation is employed, even in the presence of infection.

Packing of Mediastinum in the Treatment of Hematemesis Due to Esophageal Varices. JOHN H. GARLOCK, AND MAX L. SOM. New York State J. Med., 50, no. 2: 197, January, 1950.

The authors report further experiences in the treatment of hematemesis due to esophageal varices by packing of the mediastinum. The operation has been extended to a second stage procedure which includes a right thoracic exposure of the entire posterior mediastinum from the arch of the aorta to the diaphragm, with insertion of a gauze packing surrounding the esophagus. The purpose of this procedure is to cause the development of periesophageal granulation tissue in the hope that the venous load in the submucosal vessels will be shifted to the new vessels created by the packing operation around the esophagus. The results, thus far, are very encouraging and the authors feel that this simple procedure should be undertaken in many cases before seriously considering the operation of portocaval shunt.

Visualization of the Coronary Circulation During Angiocardiography. ALVIN J. GORDON, SIGMUND A. BRAHMS, AND MARCY L. SUSSMAN. Am. Heart J., 39: 114, January, 1950.

The coronary arteries and the coronary sinus may occasionally be identified in films taken during routine angiocardiography in man. The coronary arteries are visualized only in children. The right coronary artery was identified four times and could be traced to the sinus of Valsalva. The left anterior descending coronary artery was identified only once in

the series of over 1200 angiocardiograms. The circumstances under which these vessels may be identified are described.

The coronary sinus occasionally fills in retrograde fashion from the right auricle, in adults. Two such cases are presented. Representative roentgenograms are shown.

A Blood Vessel Bank Under Military Conditions. ELLIOTT S. HURWITT. Mil. Surgeon, 106: 19, January, 1950.

Review of the casualty statistics in World War II indicates that the methods of blood vessel repair available at that time did not result in an appreciable reduction in the incidence of amputations secondary to vascular wounds of the extremities, in comparison to techniques utilized in World War I. The principles of the transplantation of preserved arterial segments are presented. The application of this method to the treatment of casualties with arterial injuries is suggested, and a tentative program outlined.

Toxicity of Eugenol: Determination of LD50 on Rats. H. A. SOBER, F. HOLLANDER, AND E. K. SOBER. Proc. Soc. Exper. Biol. & Med., 73: 148, January, 1950.

Prior to the clinical application of eugenol for the study of mucus secretion and gastric cytology, it was necessary to estimate the limits of safe dosage. A study on dogs had revealed a maximum safe dosage of about 0.2 g/kg body wt., when an aqueous emulsion was administered. The present report presents a more precise estimation of the toxicity; i.e., determination of LD50 carried out on a large number of animals. The LD50 for pure eugenol, administered to rats by stomach tube, and without subsequent reaspiration, was estimated to be 1.8 ml. (1.93 g/kg). Any use of this datum as a guide to safe dosage in man, however, may take cognizance of the fact that the conditions of the rodent studies were considerably more severe than any which might be encountered in clinical studies. The main toxic manifestation of eugenol in the rat was paralysis, occurring initially in the hind legs and lower jaw, and frequently followed by general prostration or coma. Gross and microscopic observations of the tissues suggested that profound changes in fluid distribution occurred in response to acute irritation of the gastrointestinal tract.

Quantitative Blood Flow Measured Calorimetrically in the Human Toe in Normal Subjects and in Patients with Residua of Trench Foot and Frostbite. MILTON MENDLOWITZ AND HAROLD A. ABEL. Am. Heart J., 39: 1, January, 1950.

Blood flow in the human toe after vasodilatation by heat was studied calorimetrically in a group of twenty-three normal subjects and in a group of forty-one patients with residual symptoms of trench foot and frostbite. The average normal blood flow was 0.191 grams per square centimeter per minute \pm standard deviation of 0.041. The average blood flow in patients with trench foot and frostbite was 0.155 grams per square centimeter per minute \pm standard deviation of 0.045. The significantly decreased blood flow in the latter group is believed to be attributable to organic obstruction or constriction of the small arteries of the foot.

Use of Dried Bovine Hemoglobin Powder in the Anson and Mirsky Methods for Pepsin and Trypsin. D. ORRINGER, F. U. LAUBER, AND F. HOLLANDER. Science, 111: 88, January, 1950.

A modification in the preparation of substrates for the Anson and Mirsky methods for pepsin and trypsin determination is described. By simple solution of commercially available lyophilized beef hemoglobin, the tedious processing of fresh blood in the preparation of substrates is eliminated without affecting the reliability of the analytical results of the methods.

Fluorophotometric Estimation of Aureomycin in Blood and Urine. A. SALTZMAN. J. Lab. & Clin. Med., 35: 123, January, 1950.

Aureomycin is estimated in blood and urine by a simple chemical procedure. The antibiotic is separated from interfering substances by adsorption on a column of Decalso, which is then washed with limited amounts of distilled water, followed by ethanol and air drying.

Elution is performed with hot 5% sodium carbonate. In alkaline solutions, aureomycin fluoresces a bright blue under ultraviolet light. The fluorescence of the aureomycin in the eluate is directly measured in a fluorophotometer.

Sigmoidoscopy and Biopsy. R. TURELL AND B. J. GARSON. New York State J. Med., 50: 89, January, 1950.

The indications, contraindications, and technic of sigmoidoscopy and biopsy of recto-sigmoidal lesions are described and illustrated.

Peliosis Hepatis. F. G. ZAK. Am. J. Path., 26: 1, January, 1950.

Peliosis hepatis is characterized by the appearance of minute blood-filled cysts in the liver and occurs mainly in people who die of tuberculosis. The first case in the English literature is reported. Study of serial section was necessary to elucidate some of the points. Miliary necroses of the liver occurring in wasting diseases apparently are the necessary precursors of the peliotic lesion. The pertinent literature is reviewed and tabulated.

Emotional Stress in Relation to Attacks of Multiple Sclerosis. R. M. BRICKNER AND D. J. SIMONS. Research Pub. A. Nerv. & Ment. Dis., 28: 143, February, 1950.

A study has been made of the records of 50 cases of multiple sclerosis, in a search for distinct clinical evidence as to whether emotional factors may precipitate attacks of the disease. Clinical evidence, although not scientifically final, does suggest an affirmative answer. Difficulties are inherent in the evaluation of the evidence in many cases, and certainly is difficult to achieve. Sometimes the time interval between the occurrence of the emotional event and the development of the pathological neurological process is very short; these instances support the assumption that physiological factors linked with the emotional episodes may set off the pathological mechanism. In other cases the time interval is so long that other (physical and chemical) processes, such as anorexia or gastrointestinal disturbances are likely to occur; these, rather than the emotional process itself, must be thought of as contributing to lesion formation. The evidences are sufficiently indicative of a direct or indirect relationship between stress and the precipitation of attacks to warrant doing everything possible to help patients with multiple sclerosis to avoid stress and tension. There is not the remotest reason for considering multiple sclerosis a psychogenic disease. The most that can be said is that emotional factors may be of importance in provoking attacks, or in abetting regression.

Aureomycin in the Treatment of Experimental and Clinical Infections with H. Influenzae, Type B. C. A. CHANDLER AND H. L. HODES. Ped., 5: 267, February, 1950.

Aureomycin, in doses of 20 mg./kg. body weight, was as effective in the treatment of mice infected with H. influenzae, type B, as streptomycin and dihydrostreptomycin, and more effective than polymyxin or Q-19. Two infants with H. influenzae, type B, meningitis were treated successfully with aureomycin and sulfadiazine. Spinal fluid cultures became negative and marked clinical improvement occurred within 48 hours. Both patients recovered completely. Three children were treated with aureomycin alone. Although their response to treatment was not so rapid as that of the infants treated with aureomycin and sulfadiazine, recovery was assured within four to seven days and subsequently there were no evidences of residual damage. No serious toxic reactions to aureomycin were apparent. A sixth patient, desperately ill, succumbed within 36 hours in spite of adequate treatment with combined aureomycin and sulfadiazine.

Cranial Chordoma. J. FREEMAN. Arch. Otolaryng., 51: 237, February, 1950.

Chordoma is a locally malignant tumor found along the craniosacrocoecal axis. It is derived from notochordal remnants. Cranial chordoma presents no characteristic clinical picture and must be considered in the differential diagnosis of intracranial and nasopharyngeal tumors. Diagnosis is made by tissue examination. Roentgenologically the tumor

may or may not show calcification. It produces varying degrees of bone destruction and may invade the paranasal sinuses, the nasopharynx and the bony orbits. Endocrinopathy does not rule out the presence of this tumor. Treatment of chordoma is surgical. Radiotherapy is of doubtful value. Two cases are discussed which reveal the perplexing clinical picture of this disease.

Color Reaction Distinguishing Between Adrenalin and Nor-Adrenalin. B. KISCH. *Exper. Med. & Surg.*, 8: 1, February, 1950.

The authors nitrite reaction, which turns adrenalin solutions red, turns nor-adrenalin solution, if very little nitrite is added (5 cc solution 0.2 cc m/5 NaNO_2), to a color which contains a red and a yellow component from the beginning. If higher concentrations of nitrite are added (5 cc solution 0.2 cc of 5m NaNO_2) the red component cannot be assayed except by photospectrometric examination. Finally, after days and weeks both the nitrite reaction of adrenalin and nor-adrenalin turned to a yellow color. It is supposed that the difference in the oxydability of the OH groups in both these compounds may also be the reason for the different physiological action.

Alternation in the Electrocardiogram of a Three and One-Half Month Old Infant. B. KISCH AND B. RICHMAN. *Am. J. Dis. Child.*, 79: 326, February, 1950.

A child 14 weeks of age with a heart rate of 160 to 170 and a respiratory rate of 50, convalescing from pneumonia, showed an alternation of R, S and T waves in several of the chest leads. This is the first time that alternation has been registered in an infant of this age.

Multiple Myeloma. I. H. PARNES. *New York State J. Med.*, 50: 3, February, 1950.

A case report of a 92-year-old white woman with multiple myeloma, established clinically and proved by autopsy, is discussed. This is a case report of the oldest known patient to have had multiple myeloma. The chief complaint was bone pain in the region of the hip and various ribs. The patient lived fifteen months after onset of symptoms. No treatment was given other than symptomatic therapy.

Technic for Measuring Cardiac Output Directly by Cannulation of the Pulmonary Artery.

R. D. SEELY, AND D. E. GREGG. *Proc. Soc. Exper. Biol. & Med.*, 73: 269, February, 1950.

In the past, cardiac output has been measured directly in the experimental animal by inserting flow meters into the aorta, or into the venae cavae. Such procedures, however, do not determine total cardiac output, since they fail to measure coronary flow. To avoid this difficulty, a technic by which the pulmonary artery may be cannulated and flow through it measured has been devised for use in the anesthetized dog.

Quinidine Allergy. S. SIEGAL, AND H. HORN. *Am. Heart J.*, 39: 302, February, 1950.

Two instances of allergy to quinidine sulfate are described. The first patient manifested repeated episodes of chills and fever to 104°F ., associated with thrombocytopenic purpura. These were proved to be due to quinidine allergy by the reproduction of the clinical picture and thrombocytopenia following a single oral dose of 0.2 Gm. of quinidine sulfate. Reaction to the scratch test with quinidine was negative. A febrile reaction without purpura likewise followed the oral administration of 0.6 Gm. of quinine sulfate. The second patient's reaction was characterized by low-grade fever and pruritic maculopapular eruption induced by quinidine sulfate on two occasions. Allergy to the cinchona alkaloids is briefly reviewed and the practical management of quinidine allergy discussed.

Simultaneous Occurrence of Plasma Cell Multiple Myeloma and Hodgkin's Disease. B. B.

GREENBERG, D. STATS, AND M. GOLDBERG. *New York State J. Med.*, 50: 305, February, 1950.

This presentation contemplates the possibility of a relationship between Hodgkin's disease and multiple myeloma. Two cases are presented. In the first case, bone marrow punctures and lymph node biopsy performed at the same time revealed unmistakable evidence of plasma cell multiple myeloma in the former and Hodgkin's disease in the latter. The second case was known to have Hodgkin's disease for 10 years after which pathognomic evidence of plasma cell multiple myeloma was found. Tissue examination at autopsy in this case failed to reveal any changes of the initial disorder. In view of the simultaneous occurrence in the first case and their successive occurrence in the second, the authors suggest that the reticulum cell may be the common ancestral cell for Hodgkin's disease and multiple myeloma.

Postoperative Anal Stenosis. R. TURELL. Surg., Gynec., & Obst., 90: 231, February, 1950.

In this paper an original technic of anoplasty for the correction of postoperative anal stenosis is described. The results obtained in the treatment of over 30 such cases are presented.

Alkaline Phosphatase in Experimental Biliary Cirrhosis. M. WACHSTEIN, AND F. G. ZAK. Am. J. Clin. Path., 20: 99, February, 1950.

The histochemical distribution of alkaline phosphatase was studied in the livers of rabbits and dogs, some of which were kept alive up to 10 months after ligation of common and cystic ducts. Serum and urine enzyme studies could be correlated to a varying degree with the histochemical observations. No evidence was found for bile capillary rupture as an important factor in obstructive jaundice. The evidence at hand favors the role of the liver as that of an excretory organ rather than as a place of alkaline phosphatase production. The pertinent literature is reviewed.

Correlation of Insulin Test Studies and Clinical Results in a Series of Peptic Ulcer Cases Treated By Vagotomy. V. WEINSTEIN, F. HOLLANDER, F. U. LAUBER, AND R. COLP. Gastroenterology, 14: 214, February, 1950.

The results of postoperative insulin tests are presented in a series of 123 peptic ulcer patients treated by vagotomy with or without gastroenterostomy or subtotal gastric resection. Positive postoperative tests were obtained in 29 per cent of the cases. Reports of studies from other clinics are presented and indicate similar experience. The large percentage of physiologically incomplete vagotomies may be due to marked variations in the anatomy of the vagus nerve. The existence of non-vagal cholinergic secretory pathways is considered. Clinical results, analyzed with regard to both ulcer healing and motor disturbances, show no correlation with postoperative insulin test data, and similar experiences of other investigators in this regard are cited. The significance of this discrepancy is discussed, particularly its importance as evidence against the psychosomatic theory of ulcer etiology which postulates a gastric hypersecretion of vagal origin. It is emphasized that the insulin test cannot be used to prognosticate clinical results of vagotomy.

Incidence of Cardiac Enlargement In Nondisabling Rheumatic Valvulitis. ARNOLD L. BACHMAN. Am. Heart J., 39: 405, March, 1950.

During the careful physical examination of approximately 47,000 young soldiers to determine their fitness for flying, cardiac murmurs which were considered as being caused by organic rheumatic valvulitis were found in 82 examinees. None of these 82 men showed any evidence of impaired cardiac function. A roentgenographic cardiac abnormality was observed in 34 (41.5 per cent) of these 82 examinees. Enlargement of the left auricle was observed in 24 (29.3 per cent). Roentgen ray cardiac abnormalities were seen more frequently when multiple valves were involved or two murmurs over one valve was heard than when a single murmur over a single valve was observed. The study indicates that the

significance of cardiac enlargement in the diagnosis of rheumatic heart disease must be re-evaluated in relation to the cardiac functional status of the patient. It is evident that roentgenographic methods are of distinctly limited value for the exclusion of the possibility of organic valvulitis in persons having cardiac murmurs, but essentially normal functional capacity of the heart. On the other hand, when cardiac enlargement is found in such persons, it is of definite aid in establishing the organic nature of the murmur.

The Mechanism of Estrogen Inhibition of Comb Growth in the Cockerel, with Histologic Observations. N. F. BOAS, AND A. W. LUDWIG. *Endocrinology*, 46: 299, March, 1950.

The administration of α -estradiol to immature male chicks prevents the normal growth and development of the comb. Histological examination of the combs of estrogen-treated birds revealed the failure to deposit the metachromatic interstitial ground substance normally seen and the persistence of the immature undifferentiated structure. α -Estradiol failed to diminish the comb growth response produced by testosterone and gonadotropins, indicating that estrogenic inhibition of comb growth is dependent on the suppression of gonadotropin secretion in the adenohypophysis.

The Carotid Canal As a Pathway for Extension of Infection in the Temporal Bone. J. G. DRUSS. *Ann. Otol., Rhin., & Laryng.*, 59: 166, March, 1950.

The close proximity of the carotid canal to the tympanic cavity, the petrosa, and other structures in the temporal bone makes it particularly susceptible to the infections which occur in all these structures; and because the carotid artery with its plexus of veins lodges there, it plays a significant role in the transmission of these infections to other parts of the body. The histologic features of the carotid canal and its contents and of the neighboring structures relevant to the spread of infections are presented. Emphasis is placed upon the significance of keeping in mind, in the treatment of otitic infections, the possibility of carotid canal involvement, particularly that of thrombophlebitis of the carotid plexus of veins.

Newer Methods in the Diagnosis of Viral Diseases. A. L. FLORMAN. *N. Y. Med.*, 6: 15, March, 1950.

This is a review article emphasizing the available serological techniques for the specific diagnosis of viral infections.

Evaluation of the Mumps Skin Test. A. L. FLORMAN, A. E. FISCHER, AND R. E. MOLOSHOK. *Pediatrics*, 5: 469, March, 1950.

An intradermal test with formalin-inactivated egg-grown mumps virus was done on 109 household contacts of 42 cases of epidemic parotitis. Sixty of these individuals were skin-test positive and 49 negative. There were 12 contact cases of epidemic parotitis and 11 of them occurred among the nonreactors. There were 27 children who gave negative skin tests and they furnished 10 of the contact cases. The various types of reactions encountered are described and the frequent occurrence of relatively faint reactions in children noted. The validity of the test was supported by an obvious correlation with the incidence of secondary cases, past history and the fact that patients who were originally skin-test negative were positive several months later. It is concluded that the test is of value in determining susceptibility to epidemic parotitis. In view of the large number of clinically unapparent cases, the skin test should prove most useful in removing unnecessary concern for infection by parents who do not recall having had the disease.

Rhinoplasty: Surgical Complications and How to Avoid Them. I. B. GOLDMAN. *J. Internat. Col. Surgeons*, 3: 285, March, 1950.

The author reviews the common complications that are seen following rhinoplasty. The complications are discussed in detail and sequentially. The correction of surgical errors

is stressed. Pre-surgical planning is obviously of assistance in the correct diagnosis of specific nasal deformities and is contributory to a final esthetic result.

The anatomic structure and function must be constantly kept in mind. Sacrifice of vestibular skin with subsequent scar formation leads to distortion and interference with nasal respiration. Excessive removal of cartilage also causes distortion of the nasal tip and consequent nasal obstruction. The removal of the hump must be performed circumspectly, if the hump is inadequately removed not only does the excessive use of the rasp provoke infection but the resultant periostitis produces dorsal irregularity and may even obliterate the planned naso-frontal angle. Excessive removal of the hump produces a bony saddle and immediate correction becomes exigent. Irregularities of the dorsum are also caused by an uneven elevation of skin and periosteum over the nasal pyramid when the correct plane is not entered; incomplete removal of cartilage and debris also contribute to the irregularities. Proper trimming of the upper lateral cartilages must be accomplished so that they do not override the septum. On the other hand, excessive removal results in cicatrization between septum and cartilage with production of a "pinched" effect of the nose as well as interference with nasal breathing. The management of the lobule is a complicated one owing to the diversity of esthetic and inherent anatomic problems. The complications which follow are chiefly attributed to incorrect or careless undermining and indiscriminate removal of vestibular skin and cartilage. Various deformities which sometimes follows are corrected or minimized by skin grafts and cartilaginous implants.

Postsurgical complications are uncommon and when they occur should be treated conservatively. Prophylactic chemotherapy is especially indicated in examples of excessive tissue trauma and tissue transplants.

The Diagnosis of Early Cancer of the Colon and Rectum. E. GRANET. Am. J. Digest. Dis., 17: 95, March, 1950.

Delay in the diagnosis of early rectal and colon cancer is due to the patient's procrastination in reporting for examination when large bowel disturbances occur. The physician fails to diagnose early lower bowel cancer because of errors of omission, i. e., he fails to take and evaluate an intelligent history and to follow this with proper examination. Cardinal symptoms of colon and rectal cancer include: 1. Blood in the stool. 2. Change in the usual pattern of bowel habit. 3. Pain and tenesmus. 4. Constitutional symptoms. Cancer of the rectum and colon is not a geriatric disease. It occurs commonly in the young. Eighty per cent of recto-colonic cancers can be diagnosed by physical examination. They can be palpated with the examining finger or can be visualized through the proctosigmoidoscope. When symptoms are present and are not accounted for by sigmoidoscopic examination, a diagnostically adequate barium enema examination is mandatory. Polyps are premalignant lesions and should be removed when found. Purportedly benign chronic anorectal lesions such as fistulas, papillae and fissures are sometimes premalignant and are best excised.

Roentgenograms of the Chest. S. L. HALPERN. J. A. M. A., 142: 924, March, 1950.

Serious abnormalities of the chest, especially in persons over 35, may be missed even in a postero-anterior roentgenogram of good technical quality. For example, a lesion of significant size may lie hidden behind the cardiac shadow. Symptoms in such cases are not always referable to the thoracic cavity. In routine roentgenographic surveys of chests, a small but significant percentage of pathologic processes may be missed. This limitation requires further elucidation. No diagnostic evaluation of a patient with obscure disease can be considered complete unless a lateral roentgenogram of the chest has been taken.

Meckel's Diverticulum, Intussusception, Peritoneoscopy, Operative Cure. M. S. HARTE, AND M. G. ELIAS. Am. J. Digest. Dis., 17: 82, March, 1950.

A unique case is presented which leads to a discussion of Meckel's diverticulum, intussusception and hemorrhage. The case is one in which 1) a complication (sealed omental)

evisceration of 2) a diagnostic procedure (peritoneoscopy) led to the discovery of 3) a complication (hemorrhage) of 4) a probable complication (intussusception) of 5) the basic anomaly (Meckel's diverticulum). From the literature as well as the experience resulting from the case presented, the conclusion is drawn that the anomaly of Meckel's diverticulum must be considered for diagnosis when even one lone stool positive for blood is found with no other etiology available i.e., by exclusion. The authors feel that when not contraindicated, Meckel's diverticulum should be looked for and removed during the routine celiotomy.

The Ultimate Fate of the Graft. HERBERT M. KATZIN. *Am. J. Ophth.*, 33: 35, March, 1950.

A successful corneal transplant is one in which the donor cornea is a framework which the host's cornea gradually fills in with its own cellular elements while maintaining the original matrix. In the first few days after a corneal transplant, edema occurs at the cut edges involving the host as well as the donor. The epithelium proliferates and fills in the gap between the host and graft and fibrin fills in the posterior margin. Bowman's membrane persists and is not regenerated. The stroma and Descemet's membranes appear to remain unaltered. It is apparent that all cellular elements of the graft which are replaceable undergo quick substitution by the host. Clinical success depends upon the rapidity with which this process of replacement occurs. If the host's cornea is badly scarred or vascularized, the graft is invaded by connective tissue and does not remain clear.

Reflex Cardiac Inhibition in the Ganoid Acipenser Sturio. B. KISCH. *Am. J. Physiol.*, 160: 552, March, 1950.

In the ganoid Acipenser reflexes inhibiting the heart beat and the respiration can be provoked as in other fishes (teleosts and Selachians). The sensitivity of the skin of the sturgeon concerning these reflexes decreases from the head to the tail. The inhibitory reflexes were studied electrocardiographically. A longlasting paralyzing effect of cutting the tail of eels is described. The physiological meaning of this kind of reflexes in fishes is discussed.

Pathology of Removed Corneal Sections. J. LAVAL. *Am. J. Ophth.*, 33: 32, March, 1950.

The purpose of the study was to determine the type of corneal changes which are present in those patients who had a corneal graft operation. The specimens were all from the Eye Bank. We have been examining the discs of recipient corneas sent to the laboratory with the idea that, from the pathologic changes in the various layers of the recipient cornea, we can determine which factors will influence "a take". We have found the corneal epithelium changed in each of its five layers, but mostly in the columnar cell layer and in the outermost flattened layer which may at times be keratinized. Bowman's membrane has been found to be absent or else quite thickened or irregular in diameter. The stromal fibers are irregularly placed and the fixed cells and the wandering cells are usually increased in number. Occasionally small blood vessels are found in the corneal stroma. Descemet's membrane and the endothelium are absent, as a rule, having been lost when the disc was removed from the recipient's cornea. Dense and diffuse corneal opacities have an unfavorable influence on the results of operation. The reasons why corneal grafts fail to remain clear in completely opaque corneas are not fully understood. One explanation which has been given for the poor results in this type of cornea has been that there are not enough normal corneal cells surrounding the graft. This explanation is probably not correct, however, for clear transplants can be obtained in corneas in which all of the original cells have been destroyed by freezing, if sufficient time is allowed for corneal edema to subside and new cells to grow in.

Use of Anticoagulant (Dicumarol) in Preventing Post-Irradiation Tissue Changes in the Human Lung. Preliminary Report. S. H. MACHT AND H. J. PERLBERG. *Am. J. Roent.*, 63: 335, March, 1950.

Cases of esophageal cancer have shown complete tumor destruction, proven at autopsy,

after 5,500-6,500 roentgens tumor dose by rotational radiotherapy. Death is paradoxically caused by irradiation changes in the lung (Kaplan and Etkin). Experimentally, heparinized rabbits after irradiation showed a marked diminution of both gross and microscopic pulmonary changes as compared to a control group (Boys and Harris). Anticoagulant therapy during irradiation was proposed by the authors. A case of inoperable esophageal carcinoma is reported in which, under dicumarol, only one half the desired tumor dose was delivered before the patient's demise. Macroscopic and microscopic examination showed marked tumor destruction without radiation effect on the lungs. Eight additional cases treated, two carcinomas of the esophagus and six lung carcinomas showed no roentgen manifestations of radiation reaction up to five months after radiation. All but one lung case died. Autopsy in three cases showed no aberrant pulmonary changes due to irradiation. The authors feel that dicumarol will prevent radiation reaction in normal lung up to skin tolerance. They warn that it is difficult to maintain these patients at a constant prothrombin level and thus advocate hospitalization during the course of therapy.

The Treatment of Heart Failure: Digitalis and Mercurial Intoxication, Penicillin, Dicumarol, Major Surgery. A. M. MASTER, H. L. JAFFE, AND W. R. DORRANCE. New York State J. Med., 50: 553, March 1950.

The therapy of congestive failure is reevaluated and the following points are emphasized: (1) The danger of digitalis intoxication, particularly with digitoxin in the doses ordinarily advised. The need for caution and individualization in dosage is stressed. (2) The danger of producing the syndrome of salt depletion and dehydration in elderly persons by means of mercurials, particularly when given frequently as recently suggested, and by restricting salt. Weakness, depression, mania or even death may ensue. In this age group doses of 1 cc. should be given at less frequent intervals and periodic determination of the blood urea and sodium made. (3) Penicillin and dicumarol should be given routinely in severe cases of congestive failure. (4) Cardiac patients usually tolerate operation very well, if coronary insufficiency is avoided, and the removal of an irritating focus, such as a diseased gall bladder or fissure-in-ano, often causes remarkable improvement in the cardiac status.

Relation of Lymphocytic Infiltration of Inflammatory Origin to Angiogenesis. E. MOSCHOWITZ. Arch. Path., 49: 247, March, 1950.

Evidence has been submitted that in a wide variety of chronic granulomas autochthonous formation of new blood vessels is the rule and that it occurs in the course of a fibroblastic differentiation of the newly formed mesenchyme. This mesenchyme is formed primarily from lymphocytes that exude from blood vessels and to a lesser extent from fixed connective tissue cells which undergo a transformation. The mechanism of the angiogenesis represents a reversion to that which occurs in the embryo. The hyperplasia of the sinuses and the extramedullary blood formation in "congestive" splenomegaly are explainable in this interpretation. One of the functions of the lymphoid cell in chronic inflammation is its potentiality for being transformed to endothelium, and hence for angiogenesis. The newly formed vessels either persist or become destroyed. In the latter case the component cells revert to collagen and eventually to sclerotic connective tissue. The whole is viewed as part of the reparative process inherent in the concept of inflammation.

Effects of Various Modes of Administration of Pyribenzamine on the Histamine Wheal and Epidermal Sensitivity Reactions. S. M. PECK, B. FINKLER, G. G. MAYER, AND T. MICHELFELDER. J. Invest. Dermat., 14: 177, March, 1950.

The mode of administration of pyribenzamine as well as the amount administered determined the effects of this drug. The drug must be delivered at the reaction site in proper concentration to be effective. Pyribenzamine ointment had little effect on the histamine wheal and flare. Oral administration, local injection as well as iontophoresis, however, reduced the histamine wheal and flare. Previous iontophoresis with pyribenzamine to normal skin did reduce epidermal reactions at the site of the iontophoresis and for a short distance in its vicinity. Quantitative excretion studies after the application of pyribenzamine to the

skin were made. When pyribenzamine ointment is applied to broken skin, it could be demonstrated in the urine but not after application to normal skin according to the method used.

Hypermetabolic States Without Hyperthyroidism (Nonthyrogenous Hypermetabolism). S. SILVER, P. PORTO, AND E. B. CROHN. Arch. Int. Med., 85: 479, March, 1950.

A series of 89 patients were studied with diseases frequently associated with high basal metabolic rates. These included cases of leukemia, multiple myeloma, malignant lymphomas, carcinoma, essential hypertension, congestive heart failure, Paget's disease, polycythemia and Cushing's syndrome. All had elevation of their basal metabolic rates ranging up to plus 90% and averaging plus 40%. Thyroid function in each was studied by the determination of the protein-bound plasma iodine and the excretion of tracer doses of radioactive iodine (I-131). These studies proved that thyroid function was normal in spite of the elevated B.M.R. and that the hypermetabolic state in these patients was not of thyroid origin, in contrast to the situation in hyperthyroidism where thyroid function is distinctly increased as measured by these tests.

Weakness of Extensor Muscles of the Wrist: An Early Sign in Hemiparesis. I. STRAUSS. Arch. Neur. & Psych., 63: 453, March, 1950.

On occasion, the physician may suspect a condition of hemiparesis which is not borne out by a routine neurological examination. Among the earliest evidences of lessened functional activity of the corticospinal tract is impaired innervation of the more recently acquired muscular functions. One of the weakest links is the ability to maintain the hand dorsiflexed at the wrist. The presence of minimal corticospinal damage can be determined by the following clinical test. I have found not infrequently that if the physician will have the patient extend the hands at the wrist on the side suspected of paresis and then with the palm of his own hand press down and ask the patient to resist him, he will find that on the side suspected of being affected, the wrist muscles will give way slowly or suddenly and the hand will drop. For comparison, he should try the same procedure on the opposite side; he will find it is with great difficulty that he can cause flexion of the wrist. This weakness of the extensor muscles of the wrist on the suspected side is definite evidence of a hemiparetic state and may even be the first and earliest sign of the development of the outspoken paresis of that half of the body.

Bacitracin Levels in the Cerebrospinal Fluid After Parenteral Injections. Bacitracin Therapy of Experimental Staphylococcal Meningitis in the Dog. P. TENG, AND F. L. MELENEY. Surgery, 27: 403, March 1950.

By intravenous or intramuscular injections, bacitracin does not readily pass through the normal blood-brain barrier and reaches the cerebrospinal fluid only in an insignificant concentration. However, when the meninges are severely inflamed, as in the case of staphylococcal meningitis, a considerably higher level of bacitracin can be obtained in the cerebrospinal fluid. In experimental staphylococcal meningitis in dogs, intracisternal instillation of bacitracin, combined with intramuscular injections, saved 63 per cent of the treated group. Deaths occurred solely in animals in which treatment was started late. The control animals all died, including the first 2 which were killed, when moribund, in order to stop further suffering. Treatment by intramuscular injections of bacitracin alone was inadequate. Four dogs so treated all died within seven and one-half hours after the intracisternal bacterial inoculation. In view of the data presented in this article, it is suggested that the intrathecal injection of bacitracin may be of value and should be tried in cases of clinical staphylococcal meningitis.

Pediatric Proctology. Review with Comment. R. TURELL. Am. J. Dis. Child., 79: 510, March, 1950.

In this paper the proctologic disorders of infancy and childhood are reviewed. The review was based on the available literature of the past 10 years coupled with comments on personal experience in the management of juvenile proctologic disorders.

Action of Lysozyme on Gastrointestinal Mucosa. K. J. WANG, R. GRANT, H. D. JANOWITZ, AND M. I. GROSSMAN. Arch. Path., 49: 298, March, 1950.

The effect of the mucolytic enzyme lysozyme on the intestinal mucosa of several animal species was studied because of the current interest in this enzyme as a possible etiologic agent in ulcerative diseases of the stomach and colon. In perfusion experiments high concentrations of the enzyme produced erosions and hemorrhages in the gastric and colonic mucosa of rats, and increased the injurious action of hydrochloric acid and pepsin in vivo. Vacuolation of the mucus of the surface epithelial cells of the stomach occurred. Lysozyme did not affect the viscosity of gastric mucus. The mechanism of this type of injurious action of lysozyme is not understood at present.

Fractures of the Vertebrae in the Aged. E. M. BICK. Geriat., 5: 74, March-April, 1950.

All fractures of the vertebrae in the aged are to a greater or lesser degree pathological fractures. Compression fractures in this age group do not require the meticulous reduction and maintenance of reduction customarily advocated in younger persons. Two or three weeks of unsupported recumbency, or in less compressed cases less time, followed by sitting and walking in a high brace or corset has proven adequate treatment. In no case have later cord symptoms or other symptoms of dysfunction referable to the fracture appeared.

Electrophoretic Studies on the Protein Distribution in Normal Human Serum. M. REINER. Acta Haemat., 3: 202, March-April, 1950.

The distribution of various protein components in normal human serum has been studied by electrophoretic analysis. Twenty "professional" blood donors formed the first group of subjects studied and sixty "family" blood donors the second group. The "family" donors represent a cross-section of a mixed adult, urban population. The figures obtained by statistical analysis of the experimental data are as follows: Albumin 56.8 ± 3.0 per cent; Alpha₁-globulin 7.2 ± 1.2 per cent; Alpha₂-globulin 8.7 ± 1.5 per cent; Beta-globulin 12.8 ± 2.3 per cent; and gamma-globulin 14.4 ± 2.4 per cent; these figures are in terms of relative concentration. The albumin/globulin ratio was 1.33 ± 0.18 .

Radiation Scoliosis: An Experimental Study. A. M. ARKIN, AND N. SIMON. J. Bone & Joint Surg., 32-A: 396, April, 1950.

Unilateral radiation was directed to the growing spine of young rabbits. This resulted in arrest of epiphyseal growth on the irradiated half of the spine. The opposite side continued to grow, resulting in the production of scoliosis. The type and pattern of scoliosis could be controlled by varying the pattern of irradiation.

Persistent Cervical Thymus Gland; Thymectomy. E. E. ARNHEIM, AND B. L. GEMSON. Surgery, 27: 603, April, 1950.

Persistence of thymic tissue in the neck associated with complete or partial failure of descent of the gland into the mediastinum is known to occur along the course followed by the thymus in its descent in the embryo from the third pharyngeal pouches. The case reported is the first persistent cervical thymus gland due to partial failure of descent in which thymectomy was performed. The patient was a male infant, aged 9 months, with tracheal compression due to pressure at the junction of the cervical and thoracic components of the thymus at the suprasternal notch. The symptoms were relieved, and follow-up studies revealed no abnormalities of growth or development.

Treatment of Disseminated Lupus Erythematosus with Cortisone and Adrenocorticotropin. G. BAEHR, AND L. J. SOFFER. Bull. New York Acad. Med., 26: 239, April, 1950.

The adrenal cortex of patients with disseminated lupus erythematosus responds normally to ACTH stimulation. It can be stated that cortisone and ACTH are life-saving in disseminated lupus erythematosus, inducing a remission of the disease even when therapy is be-

gun at a time when patients are critically ill with a serious exacerbation of the disease. They are extremely potent remedies, the use of which is accompanied by serious hazards due to rapid shifts of blood electrolytes between cells and intercellular spaces and increases in total body water sufficient to induce congestive heart failure and pulmonary edema. In some instances the systolic and diastolic blood pressure may be elevated during treatment with large doses. Therapy may induce a disturbance in acid balance sufficient to cause alkalosis. This tendency may be seriously accentuated when mercurial diuretics are administered to combat congestive heart failure, due in part to excessive loss of chlorides. Ordinarily, the sodium and potassium content of the blood of patients under treatment with this hormone remains at normal levels, but under the influence of a mercurial diuretic, potassium may be rapidly lost in the urine at a time when sodium is retained because of the influence of the cortisone. The resulting hypopotassemia may place the patient's life in serious jeopardy. It is therefore recommended that these extremely potent hormones should be used at present on patients with disseminated lupus erythematosus only in a hospital equipped with a specially trained staff and with facilities for accurate chemical and physiological measurements. Finally, it is necessary to emphasize that the dramatic improvement of the disease under therapy, even apparently complete clinical recovery, cannot be interpreted as more than a remission. The condition of these patients must still be regarded as most precarious, for the persistence of leukopenia, accelerated sedimentation rate of the erythrocytes, and the persistence of L.E. cells in the bone marrow or blood indicate that the disease is still active and the unknown cause has not been eliminated. It would seem from these observations that the administration of large doses of cortisone and ACTH to patients with disseminated lupus erythematosus prevents or arrests the abnormal enzymatic processes in mesenchymal cells initiated by an unknown causative factor. The action of these potent hormonal agents is in this sense non-specific. Hence their wide spectrum of effectiveness in a great variety of disease processes (rheumatoid arthritis, rheumatic fever, disseminated lupus erythematosus, allergies, pemphigus, wound healing, etc.) which have one thing in common, namely, that their various causative factors exert a detrimental influence primarily upon the collagenous or, in a broader sense, the mesenchymal tissues of the body.

Malformation of the Erythrocytes in a Case of Atypical Retinitis Pigmentosa. F. A. BASSEN, AND A. L. KORNZWEIG. Blood, J. Hematol., 5: 381, April, 1950.

A case is presented of a girl, aged 18, born of parents who were first cousins. She had an atypical *retinitis pigmentosa* with involvement of the macula. The neurologic examination showed diffuse disease of the central nervous system, as seen in Friedreich's ataxia. An additional finding (hitherto undescribed) was that of a malformation of the red blood cells. These cells had a peculiar crenated appearance, due to the presence of pseudopods or protoplasmic projections varying in size and shape. They were constantly present in stained blood films taken 1 year apart. A similar finding in a younger brother, with beginning retinal pigmentary degeneration, added additional proof of the hereditary nature of the condition.

Successful Removal of a Tumor Embolus from the Femoral Artery. L. BLUM. J. A. M. A., 142: 986, April, 1950.

The rarity of massive neoplastic embolism is well known. The second recorded instance of successful removal of a malignant arterial embolus is the subject of this paper. Its interest is more than statistical because the patient survived the operative procedure three months at which time autopsy made clear the pathogenesis and afforded the rare opportunity of examining the site of arteriotomy. A 60 year old restaurant worker was being investigated for a lung lesion when he suddenly suffered an abdominal crisis, which on exploration proved to be due to a spontaneous rupture of the spleen. During his convalescence there was a sudden pain in the left inferior extremity with complete loss of sensation and pallor below mid-thigh. A diagnosis of embolization of the left femoral artery at the profunda branch was made. Operation was immediately performed and the diagnosis confirmed. Section of the embolus revealed it to be neoplastic in nature. Locally the patient did very

well and was walking about by the fourth day with pulses restored. He died of malignant disease three months later. Section of the femoral artery wall through the site of arteriotomy revealed complete restitution of its architecture.

A Comparison of Electrocardiography and Roentgenkymography in the Study of Myocardial Infarction. S. DACK, D. H. PALEY, AND M. L. SUSSMAN. *Circulation*, 1: 551, April, 1950.

A description is presented of a method of recording and analysis of the electrokymogram, utilizing simultaneous recording of the electrocardiogram, heart sounds, and carotid pulse tracings as reference points to identify the events in the cardiac cycle. The electrokymogram of the left ventricle in the normal heart and in the presence of myocardial infarction is described. The electrokymogram in myocardial infarction often discloses paradoxical (lateral) movement of the left ventricular border in systole and medial movement in diastole. The clinical value in electrokymography is emphasized by the findings in two cases of myocardial infarction, in which the electrokymogram clearly demonstrated these characteristic abnormalities which the roentgenkymogram failed to disclose. The normal variations in the curves of the isometric and ejection phases are described to minimize or prevent an erroneous diagnosis of abnormal ventricular movement. It is emphasized that the electrokymogram represents a combination of volumetric and complex positional changes.

Ventricular Contraction in Wolff-Parkinson-White Syndrome: An Electrocardiographic Study. S. DACK, D. H. PALEY, AND S. S. BRAHMS. *Bull. New York Acad. Med.*, 26: 273, April, 1950.

The introduction of electrokymography has made available a simple and accurate method of determining ventricular asynchronism from the onset of the aortic and pulmonary kymographic curves which indicate left and right ventricular ejection, respectively. Normally there may be a physiological lag of ± 0.03 sec. between aortic and pulmonary artery ejection. This method has uniformly demonstrated the presence of mechanical asynchronism of the ventricles in bundle branch block, with a lag of 0.04 to 0.07 sec. between aortic and pulmonary artery ejection, depending on the bundle-branch affected. It would be expected that if ventricular asynchronism were present in Wolff-Parkinson-White syndrome a similar lag between aortic and pulmonary ejection would be observed. In an attempt to throw light on this disputed subject we have carried out detailed electrokymographic studies in 4 cases of Wolff-Parkinson-White syndrome with typical electrocardiographic features. In one case the aortic and pulmonary artery kymograms were simultaneous and in the other three cases pulmonary artery ejection preceded that of the aorta by 0.02 sec. The latter lag is within the normal physiological range. Analysis of the left and right ventricular kymograms yielded similar measurements. These observations indicate a lack of asynchronism in left and right ventricular ejection.

Further Observations on Packing of Mediastinum for Esophageal Varices. JOHN H. GARLOCK AND MAX L. SOM. *J. Thoracic Surg.*, 19: 572, April, 1950.

The authors report further experiences with the packing of the mediastinum operation in the treatment of esophageal varices. During the discussion they indicate the technique for increasing the efficiency of the operation by a second stage procedure consisting of a trans-thoracic packing of the posterior mediastinum between the arch of the aorta and the diaphragm. A number of cases are cited in which this operation was carried out. The immediate results have been promising and a further report will be made at a later date to indicate the results of long-term observation.

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CONTENTS

	PAGE
THE WILLIAM HENRY WELCH LECTURE. THE EARLY CHANGES CAUSED BY RADIATION. <i>Shields Warren, M.D.</i>	443
HISTOCHEMISTRY OF ENZYMES. <i>G. Gomori, M.D.</i>	446
RECENT OBSERVATIONS ON THE PATHOGENETIC MECHANISM OF IDIOPATHIC THROMBOCYTOPENIC PURPURA. <i>Mario Stefanini, M.D.</i> ...	452
TRANSMESENTERIC HERNIA. <i>Alfred A. Pomeranz, M.D. and Lester G. Steppacher, M.D.</i>	465
SARCOIDOSIS WITH BRONCHIAL INVOLVEMENT. A REPORT OF TWO CASES WITH BRONCHOSCOPIC BIOPSIES. <i>Louis E. Siltzbach, M.D. and Max L. Som, M.D.</i>	473
THE JEWS' HOSPITAL AND PSYCHOLOGICAL MEDICINE. <i>Joseph Hirsh and M. Ralph Kaufman</i>	481
THE OSTEOHISTOLOGY OF THE NORMAL HUMAN VERTEBRA. ITS RELATION TO SCOLIOSIS AND CERTAIN LESIONS INCIDENT TO GROWTH AND SENESCENCE, <i>Edgar M. Bick, M.D.</i>	490
ABSTRACTS.....	528
BOOK REVIEW.....	536

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THE WILLIAM HENRY WELCH LECTURE*
THE EARLY CHANGES CAUSED BY RADIATION

SHIELDS WARREN, M.D.

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The acute radiation syndrome resulting from total body irradiation has not been a problem until recent years. Only a few cases of leukemia and lymphoma had been treated in the past with total body radiation. However, with the use of the atomic bomb at Hiroshima and Nagasaki and with the complex processes involved in the development of atomic energy, large masses of people have been and are potentially exposed to radiation reaction. Moreover, now that this country has not sole control of the atomic bomb, it is important for those interested in civil defense to be aware of the acute radiation syndrome and its therapy.

The responses to total body radiation vary markedly with the dose received and with time. The median lethal dose is accepted as approximately 400 r. From experience at Hiroshima and Nagasaki, this resulted in death in 30 to 60 days.

If the amount of radiation is overwhelming, amounting to thousands of r, there is prompt death from shock in the experimental animal. We have no human pathologic material available, although undoubtedly some deaths from this overwhelming radiation occurred at Nagasaki and Hiroshima.

On the basis of the data obtained in Japan, from the Los Alamos accidents, where there were two fatalities, and much work on experimental animals, it is possible to differentiate several latter stages of the acute radiation syndrome in addition to that due to shock.

In those individuals who have received several hundred or a few thousand r of total body radiation, the second phase presents itself as one of leukopenia and atrophy of lymphoid tissue, accompanied by marked susceptibility to infection. Many of the usually nonpathogenic organisms are able to take over. Thus, extensive ulcerations may be seen produced by such organisms as *Staphylococcus albus* and *E. coli*. The oropharynx, skin, and gastro-intestinal tract are particularly involved in these infections. There may be a very high degree of bacteremia. Histologically, the lesions are characterized by an absence of polymorphonuclear infiltration. Such cells as do react are in the macrophage series chiefly.

The damage to the intestinal tract which occurs quite early because of the susceptibility of the intestinal mucosal epithelium is made manifest symptomatically by nausea, vomiting and diarrhea. By and large the earlier these symptoms appear and the more severe they are, the heavier the radiation damage has been.

In those individuals receiving fairly heavy amounts of radiation who survive the period of bacteremia a hemorrhagic phase next supervenes. Several factors are

* Delivered at the Blumenthal Auditorium, The Mount Sinai Hospital, New York, New York, January 18, 1952.

apparently involved in the hemorrhage, although thrombocytopenia is probably the most important single one. There is some evidence of alteration in capillary permeability and some evidence of disturbance of the clotting mechanism of the blood. The hemorrhage may be extraordinarily widespread and give rise to a great variety of clinical symptoms according to whether they may be intracranial, within muscles, subcutaneous, or in internal organs. Bleeding from the gums, hematuria and rectal bleeding are particularly common. The hemorrhagic phase in the Japanese survivors was most marked from the fourth to the seventh week.

Some cases which survive these earlier manifestations die from the last and rarest type of acute radiation injury—pancytopenia. Most of these deaths in the Japanese survivors occurred between the seventh and twentieth week. Most individuals surviving beyond the twentieth week recovered. In the pancytopenic phase the bone marrow may be a typical one of exhaustion or it may in some instances actually be a hyperplastic marrow with failure of maturation. The red count goes as low as 1,000,000; the white count may be only 3,000 or 4,000. Anemia and the associated anoxia are usually the presenting symptoms.

If we parallel these gross manifestations with the study of events at the cellular level, we find that the initial change is usually a cessation of mitosis. With sublethal doses, mitosis recovers to some degree in 18 or 24 hours. A very few hours after injury vacuolization of the nucleus and later of the cytoplasm appears with some swelling of the cells. During this time the Golgi apparatus tends to swell and fragment and the mitochondria also tend to swell and fragment. Many of the mitoses in the cells that survive irradiation are abnormal and may lead, in those cells that survive, to altered function and altered structure. There is usually relatively little direct radiation injury to blood vessels or supporting tissue because an insufficient dose level is obtained to bring about these changes. However, in some instances where the dose was very heavy changes have been seen comparable to those seen in the treatment of neoplasms through relatively restricted fields.

The therapy of the acute radiation syndrome is largely supportive. With overwhelming radiation, no therapy is of value. In radiation in amounts that would ordinarily be lethal, a considerable degree of protection can be obtained by various therapeutic approaches. First, it must be borne in mind that most of the individuals affected by the explosion of an atomic bomb would also have injuries resulting from the other energy releases of the bomb; for example, flash burns and blast injuries. Consequently, while there is some discussion as to whether in the uncomplicated acute radiation syndrome transfusions are of value, nevertheless, in the average case transfusions are definitely indicated. In any case of radiation injury the damage to the intestinal tract is an important factor. This impairs the absorption of oral medication as well as of food and water. Consequently, parenteral therapy must be very largely resorted to.

The antibiotics are of very material value in tiding over the period of leukopenia and enhanced susceptibility to infection.

In addition, it is important not to concentrate attention on the radiation reaction alone, but to remember that other injuries may exist and must be adequately cared for.

During the pancytopenic stage, liver extract does not seem to be of significant value and indeed beyond the supportive therapy of transfusions there seems to be little of avail.

Assuming recovery from the acute radiation syndrome, the long-range prognosis is, of course, of interest. At Hiroshima and Nagasaki, the Atomic Bomb Casualty Commission is finding an increased incidence of leukemia and cataract among the survivors within the 1000-meter zone.

However, insufficient material has been obtained as yet to have any firm statistical data.

The question of production of hereditary anomalies by a single exposure to radiation is of interest. Relatively few cases of sterility were seen among the Japanese survivors because a dose of radiation sufficient to sterilize was under ordinary circumstances sufficient to cause death. Some years will have to elapse before data on hereditary changes can be obtained in Japan.

On the other hand, by extrapolation from the experimental animal, it is probable that there will have been a significant effect on the germinal epithelium by the dose of radiation received by the survivors and that, therefore, some anomalies may well be found.

Interestingly enough, epilation is a fair prognostic sign so far as recovery from the acute radiation syndrome is concerned. Epilation occurred only with the heavier doses and was transient in those who survived. This might well be expected, as the usual epilating dose is well above the median lethal dose of total body radiation.

HISTOCHEMISTRY OF ENZYMES*

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Ever since the discovery of the paramount importance of enzymes in all biological functions there has been an ever-increasing interest in the pattern of their distribution in the tissues under various normal and pathological conditions. Recent advances in our knowledge about intracellular enzymes have been largely due to the development of new technical methods for their localization.

At the present time, there are three main avenues of approach to the localization of enzymes.

I. The first approach is simply an outgrowth of conventional biochemical methods, whether it is on a gross or on a microscopic level. On the gross level, tissue samples are dissected from their environment (for instance, tumor nodules from the liver; corpora lutea from the ovary, etc.) and the data of analysis for enzymes are compared. Such studies may reveal significant differences between the enzymatic composition of various tissues. However, since localization is only global, false conclusions may be drawn from the results. For instance, the high alkaline phosphatase content of corpora lutea has been interpreted as an indication of the role of phosphatase in the synthesis of progesterone (1). Later studies with more exactly localizing methods (2) have revealed that the enzyme is not localized in the parenchymal elements but only in the walls of blood vessels (fig. 1), and that the high activity of the structures is due only to their rich vascularization. On the microscopic level, certain cytological structures (nuclei, mitochondria, homogeneous ground substance) are separated by methods such as differential centrifugation and then analysed. In this way data are obtained in respect to the general chemical organization of the cells. It is to this body of data that the term "cytochemistry" should be applied (3); the term "histochemistry" should be reserved for the science dealing with the chemical differentiation on a cellular or tissue level.

The great advantage of biochemical methods lies in the relative accuracy of quantitation. Their greatest disadvantage is unsatisfactory localization. Another shortcoming of the biochemical method is that, for clearcut results, the individual enzymes must be obtained in a reasonably purified form. Otherwise, especially in the case of overlapping substrate specificities, the results may be hard or impossible to interpret. Let us take the following example: there are two enzymes present in a crude tissue extract, acting on the same substrate; however, while enzyme A is activated, enzyme B is inhibited by a certain chemical substance. From the data of activity obtained in the presence and in the absence of the substance mentioned it will be impossible to even detect the existence of two individual enzymes, let alone to determine their relative amounts, since activation and

* This work has been supported by grants from the Douglas Smith Foundation of the University of Chicago, and from the Pathology Study Section of the U. S. Public Health Service.

inhibition effects may cancel each other in an unpredictable way. A third drawback of biochemical methods is their inability to demonstrate high concentrations of enzyme localized in single cells, scattered sparsely among a vast majority of inactive cells. The dilution effect may cause the over-all activity of the tissue to fall below the threshold of sensitivity of the method. This point will be brought up later in connection with a specific example.

II. The second approach is the method of Linderström-Lang (4). It is based on the statistical comparison of data of chemical analysis with those of differential cell counts. The method is extremely laborious, involving the microscopic examination of scores of histological sections and the same number of very delicate chemical analyses on a micro-micro scale. In some cases the results are unequiv-

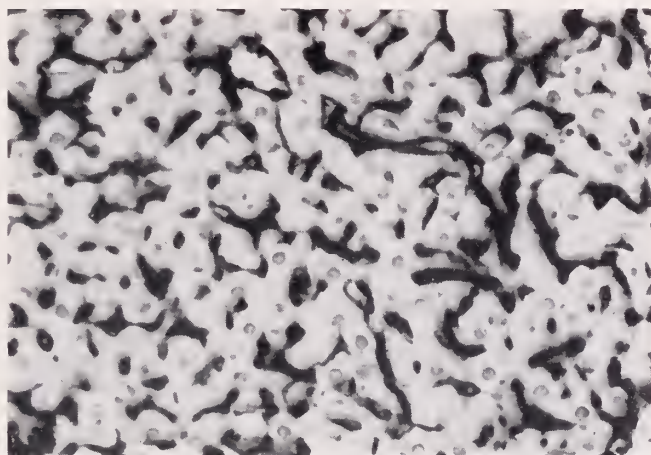


FIG. 1. Corpus luteum of the rat. Alkaline phosphatase reaction in capillary walls only.

ocal. However, this technique can be successful only under the following conditions:

1. There must be several morphologically recognizable cell types present.
2. The enzyme must be associated with only one of these cell types.
3. The enzyme must not be localized in tissue structures which do not lend themselves to morphological quantitation (connective tissue, vessel walls, nerve plexuses, etc.).

These conditions are not realized in a large number of cases; an example will be given later.

III. The last type of approach is the histochemical one in the stricter sense of the term. The principle of the histochemical method is as follows: tissue sections are made to act on suitable substrate mixtures to produce insoluble colored precipitates at the exact sites of enzymatic activity. This method presents two main difficulties:

1. Some enzymes are so labile that they do not survive the manipulations necessary to prepare microscopic sections. Although the limits of tolerance of most enzymes are fairly well known, and the methods for the individual enzymes

are so designed as to preserve activity to the fullest possible extent, it sometimes happens that the enzyme is partly or completely inactivated in the preliminary stages.

2. It is often extremely difficult to devise suitable substrate systems. Actually, methods are available only for a small number of enzymes. A good substrate must be changed enzymatically into products which are either insoluble themselves or capable of very rapid precipitation by a reagent incorporated in the substrate mixture to yield a highly insoluble compound. In some cases such ideal reactions have been devised, and the resulting localization matches in accuracy the resolving power of high power dry optical systems. In other cases these conditions cannot be realized to perfection and, consequently, the sharpness of localization is more or less blurred by diffusion artifacts.

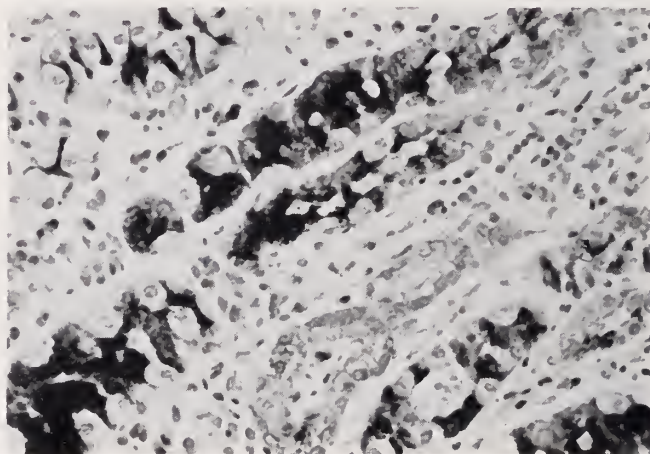


FIG. 2. Human stomach. Esterase activity (azo-dye method) in the chief cells; parietal cells inactive.

The results obtained by means of histochemical methods are an important complement to our biochemical knowledge about enzymes. As mentioned, biochemical methods have the advantage of superior quantitation, although it is possible to estimate the order of magnitude of activity even by histochemical methods (5). The histochemical method, on the other hand, affords a sharp localization. Its results in the field of enzyme localization are the most spectacular and relatively best known ones. Its contributions to normal and pathological histology are numerous, and many of them are included in standard textbooks. Only a few less well known examples will be mentioned here. It is possible to show that in the human stomach lipase and esterase are produced by the chief cells (fig. 2), while in the duodenum, by scattered individual cells, morphologically identical with their neighbors (6). It would be impossible to establish the activity of these cells by the method of Linderstrøm-Lang. The method for cholinesterase (7) outlines the conducting system of the dog's heart, the spindles of the mouse muscle and the sympathetic ganglia of the human intestine with

remarkable clarity. A special alkaline phosphatase, called 5-nucleotidase, can be demonstrated (8) in certain tracts of the central nervous system and in the smooth muscle of the blood vessels and the urinary tract. Motor ganglion cells of man, the rabbit and the rat contain large amounts of a special esterase (AS esterase (9) (fig. 3), which hydrolyzes certain naphthol esters. In the cat, on the other hand, this esterase is present in the astroglia only. This is one example of the innumerable puzzling species differences in the patterns of enzymatic activity. In pathohistology, the most interesting finding is the presence of large amounts of phosphamidase in practically all malignant epithelial neoplasms (10) and in all polyps of the colon, whether benign or malignant.

It should be emphasized that accurate localization is not the only achievement of histochemical methods. In some cases, when the enzyme is concentrated in a

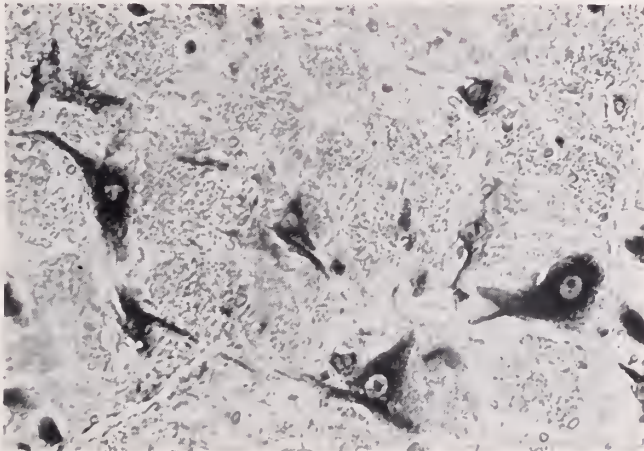


FIG. 3. Medulla oblongata of the rabbit. AS esterase reaction in the motor ganglion cells.

few highly active but small spots, the histochemical method is actually more sensitive than biochemical assay. This point is especially well illustrated in the case of macrophages which contain large amounts of AS esterase. They are stained in conspicuous brilliant red shade, seen even under the lowest powers (fig. 4), while in test tube experiments the dilution effect would wipe out all activity. In other cases histochemistry has revealed extremely interesting facts about the interrelationships between enzymes. At this point a few words must be said about differences between the biochemical and histochemical criteria of the plurality of enzymes. In biochemistry, the presence of more than one enzyme in a tissue is assumed if by chemical or physical means protein fractions with different enzymatic properties can be isolated. In histochemistry, the criterion is a change in the topographic pattern of enzymatic activity, caused by changing the conditions of incubation. To quote an example: kidney extracts when incubated with phosphoric esters display two pH optima, one around 5 and the other one around 9. Theoretically, this activity could be accounted for by a single enzyme having two

pH optima or by two enzymes, one active under acid and the other under alkaline conditions. The presence of two enzymes has been proven biochemically (11) by the successful isolation of two fractions, characterized by the pH optima mentioned. Histochemically, the evidence is the completely different patterns of localization obtained at pH 5 and pH 9, respectively. In many cases, the presence of a large number of individual enzymes in a tissue can be demonstrated relatively simply by incubating sections under varying conditions. Biochemically, the preparation of many fractions would be a formidable undertaking, and impossible whenever the amount of tissue available is small. On the other hand, histochemical methods permit the testing of a single mouse ovary for as many enzymes as we have techniques for.

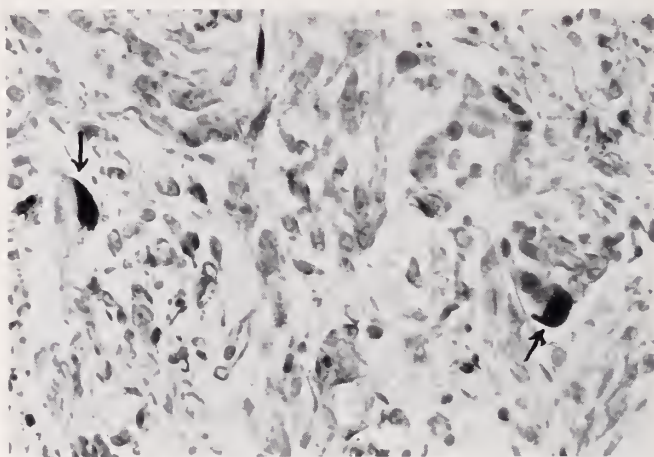


FIG. 4. Two macrophages (arrows) in a metastatic sarcoma of the lung, showing intense AS esterase activity.

The fact that in histochemistry one is able to observe localized enzymatic behavior directly under the microscope has made it possible to secure data about enzymes which could not be obtained by biochemical methods.

The visualization of small centers of high activity has been mentioned before. Another achievement of histochemistry is the resolution of some enzymes into two components. For instance, lipase of the mouse testis can be resolved into two fractions: one localized in the interstitial cells and completely inhibited by arsanilate, and a second one localized in the spermatogenic elements and insensitive to arsanilate (12). Gastric lipase of the mouse is also a composite of two fractions: the enzyme localized in certain chief cells of the fundus is activated by bile acid while the enzyme of the neck cells and of the muscle layer is inhibited by it. A third important histochemical contribution to the knowledge of enzymes concerns the classification of esterases. Although it has been suspected for some time that the original simple classification into two groups (aliesterases and cholinesterases) with two subgroups in each category (lipase and esterase, and specific and nonspecific cholinesterase, respectively) cannot be maintained rigidly, only

recent histochemical studies have revealed the real complexity of the problem (9). While the existence of certain well-defined, pure prototypes is a fact, the perplexing variety of activity patterns seen in sections of various tissues incubated under different conditions seems to indicate that most of the esterases found in the tissues are intermediates, possessing all possible combinations of the features of two or more prototypes. Accordingly, it must be assumed that esterases form a large family of closely related enzymes, differing from each other by minor details in their prosthetic groups. Proteins of related animal species may exhibit a similar multiple overlapping of their immunological properties, probably for analogous reasons.

The data presented here are quite fragmentary, and it is admitted that at this stage they cannot be interpreted and integrated in terms of biological significance. However, there can be no doubt that further developments and refinements in histochemical technique will greatly contribute to an understanding of the role of enzymes under various conditions of health and of disease.

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RECENT OBSERVATIONS ON THE PATHOGENETIC MECHANISM OF IDIOPATHIC THROMBOCYTOPENIC PURPURA*

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The observations presented to-night are but preliminary data which have been obtained in the course of a long-term study on the physiology of platelets and the pathogenetic and therapeutic aspects of platelet deficiency. In our Laboratory these problems are being met from the double approach of: (a) the study of the physical, chemical and enzymatic properties of platelets, now obtainable in large amounts and without contamination of red blood cells and leucocytes; (b) the study of the various mechanisms which regulate the production, release from the bone marrow and possibly other organs, the life span and the final disposal of platelets in normal and pathologic conditions. Many of these problems have been merely touched upon; in others, much satisfactory progress has been made.

Tocantins' excellent monograph (1) on platelets elucidates a number of chemical and enzymatic constituents of thrombocytes. Most of the data reviewed there have been confirmed with more exacting techniques. Platelets contain enzymes, among them, alkaline phosphatase, esterase and catalase. Moreover, at least three agents active in the coagulation of blood (2), serotonin (3) and, at least in the rabbit (4), histamine, are present in platelets. Little is known of the functions of thrombocytes in the general economy of the body, with the exception of their all important role in the process of hemostasis. Platelets are indispensable for the normal control of hemorrhage. They condition the prolonged generalized vasoconstriction which follows vascular injury, initiate the process of formation of fibrin and induce the retraction of the clot. We shall not now comment on the role of platelets in the pathogenesis of many hemorrhagic disorders and of thromboembolism, which we have discussed last night and which has been the subject of specialized articles (5-9). We should, however, stress the urgent necessity for investigations directed to unravel the role of platelets in body functions other than hemostasis.

It is my purpose to-day to discuss briefly some observations of other investigators and ours on the mechanism of thrombocytopenia in "idiopathic thrombocytopenic purpura" (I.T.P.). Thrombocytopenias, as a group, can be clearly differentiated into the primary, idiopathic or megakaryocytic type and the secondary, amegakaryocytic type. In both varieties the number of circulating platelets is greatly diminished and all the abnormalities of the hemostatic mechanism characteristic of platelet deficiency are found (increased capillary fragility, prolonged bleeding time, defective clot retraction, high prothrombin activity of

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† This article was prepared during the tenure of a Damon Runyon Senior Clinical Research Fellowship, administered by the American Cancer Society.

serum). The bone marrow, however, is strikingly different in the two varieties. In secondary thrombocytopenia (due to hypoplasia or aplasia of the hemopoietic tissue or to the substitution of active tissue by foreign cells) the bone marrow contains few or no megakaryocytes. In I.T.P., on the contrary, the bone marrow contains increased number of megakaryocytes, the majority of which show agranular cytoplasm and are not surrounded by platelets. This appearance of the megakaryocytes is commonly considered as evidence of their failure at platelet production (7). Within I.T.P., a further distinction is necessary between the acute and chronic types. Acute I.T.P. occurs generally in young individuals, who never before presented hemorrhagic manifestations, following medication with several substances (sulfonamides, antibiotics, etc.) or infection. Purpura, in this case, develops suddenly and is severe. The responsible mechanism seems to act simultaneously: (a) inhibiting platelet production from the megakaryocytes; (b) accelerating the rate of disappearance of circulating platelets, and (c) injuring the capillary wall. In the first stage of the disease, platelets are strikingly decreased, the bleeding manifestations in the skin and from mucous membranes are severe, the bleeding time is much prolonged, the capillary fragility greatly increased, and the megakaryocytes of the bone marrow appear "inactive". Later on, although the platelet count remains low, hemorrhagic manifestations begin to subside and the bleeding time and capillary fragility improve. Finally, the platelet count begins to rise and bleeding manifestations ordinarily stop altogether. The entire duration of the process is two weeks to a few months. Most of the cases, therefore, are cured spontaneously and only a few assume a chronic course. The platelet count remains at subnormal levels and drops, at intervals, to low values when bleeding manifestations may recur.

The chronic variety of I.T.P. develops in adults who present bleeding manifestations of less sudden onset and less severe nature, together with thrombocytopenia. The disease progresses with alternating phases of improvement and exacerbation of the bleeding symptoms, although the platelet count remains subnormal even during apparent clinical remissions. Ultimate spontaneous recover is the exception; between 60 and 70% of these patients are cured by splenectomy, the rest responding to the operation only with a temporary elevation of the platelet count. Even when failing to normalize the platelet count, splenectomy, however, reduces the bleeding tendency. Acute and chronic varieties of I.T.P. appear clinically so much different that it could be postulated they are due to entirely different pathogenetic mechanisms.

Two years ago, preliminary observations indicated to us that the rate of disappearance of platelets injected into the circulation was strikingly different in patients with I.T.P. and patients with secondary thrombocytopenia. The decision to continue this investigation met with the difficult task of developing a technique which would allow the transfusion of large numbers of platelets in a short period of time. After many trials, we finally adopted a technique of direct multiple-syringe transfusion of platelet-rich polycythemic blood or plasma into the recipient, a method which has been used by Doctor William Dameshek since 1925. Syringes and needles were, of course, coated with the water-repellent film

Silicone (Dri Film 9987, General Electric Company). Donors used were perfectly compatible in group and type with the recipient. In order to avoid as much as possible incompatibility of the donor's platelets with the recipient's serum, the donor's blood was accepted only after we failed to demonstrate in the serum of the recipient the presence of agglutinins and lysins against the platelets of the donor. The following techniques were used: (a) inactivated and decalcified serum of the recipient was added to an equal volume of suspension of the donor's platelets both in their own plasma and in 0.2 M solution of sodium citrate containing 0.2 Gm. per 100 ml. of sodium acetate. Evidence of macroscopic and microscopic agglutination was sought for at the end of 2 and 18 hours of incubation at room temperature in Silicone-coated test tubes; (b) to the platelet-serum mixture we added 0.02 ml. per ml. of reconstituted human complement, freshly prepared. Platelet counts were taken immediately, and again after 2 hours of incubation at room temperature. All recipients' sera examined failed to exhibit agglutinating or lytic activity. Before, and at various intervals of time after the transfusion, platelet counts by direct and indirect methods, clot retraction, bleeding time, tourniquet test and prothrombin activity of serum were followed in the recipient. Techniques of these determinations and detailed results have been presented elsewhere (8). In summary, the rate of disappearance of platelets was 1 to 4 days in cases of secondary thrombocytopenia, but much more rapid (1 to 12 hours) in I.T.P. (fig. 1). Retraction of the clot and prothrombin activity of the serum followed closely the changes in the platelet count, while bleeding time, tourniquet test and the bleeding manifestations themselves remained improved for some time (12 hours to 2 days) even after the platelet level had returned to the low original level. Surgeons who performed splenectomy in patients with I.T.P. a few hours after a transfusion of platelet-rich blood encountered less bleeding during the first part of the procedure (bleeding in these patients has a tendency to diminish strikingly following the ligation of the splenic pedicle). A few more technical details should also be given here. To reduce the "hunger" of the tissues for platelets which presumably exists in thrombocytopenia, the patients selected for direct transfusion were given a preliminary transfusion of approximately 6 ml./kg. weight of fresh citrated blood within 3 hours of its collection, containing approximately $\frac{3}{5}$ of the original platelet level of the donor. Not later than four hours after the preliminary transfusion, the patient received a direct transfusion of platelet-rich blood in the volume of approximately $\frac{1}{10}$ of his calculated blood volume. By injecting blood containing 1.5-2 millions or more platelets per ml. with a loss not greater than 10-20% during the procedure, a rise in the original platelet count was obtained in all cases and the rate of disappearance of the platelets from the circulation could be determined. As already stated, the disappearance of injected platelets in I.T.P. was very rapid. It was found roughly related to the original degree of thrombocytopenia of the patient. Thus, in patients with higher platelet counts, the rate of disappearance of platelets was rather slow when compared to patients with severe thrombocytopenia. In cases of chronic I.T.P. the rate of disappearance of injected platelets was also slow and these patients presented a much higher count than cases of acute I.T.P. This is

an understandable finding, since the platelet level found in patients with I.T.P. very likely represents an equilibrium between production and utilization or destruction of platelets. These experiments have been performed to date in 31 patients for a total of thirty-seven direct transfusions, with similar results.

The rapid disappearance from the circulation of patients with I.T.P. of injected platelets could be explained by a number of factors, such as: (a) the increased utilization of platelets due to the wide-spread, severe injury of the capillary wall; (b) the sequestration and destruction of platelets in various organs;

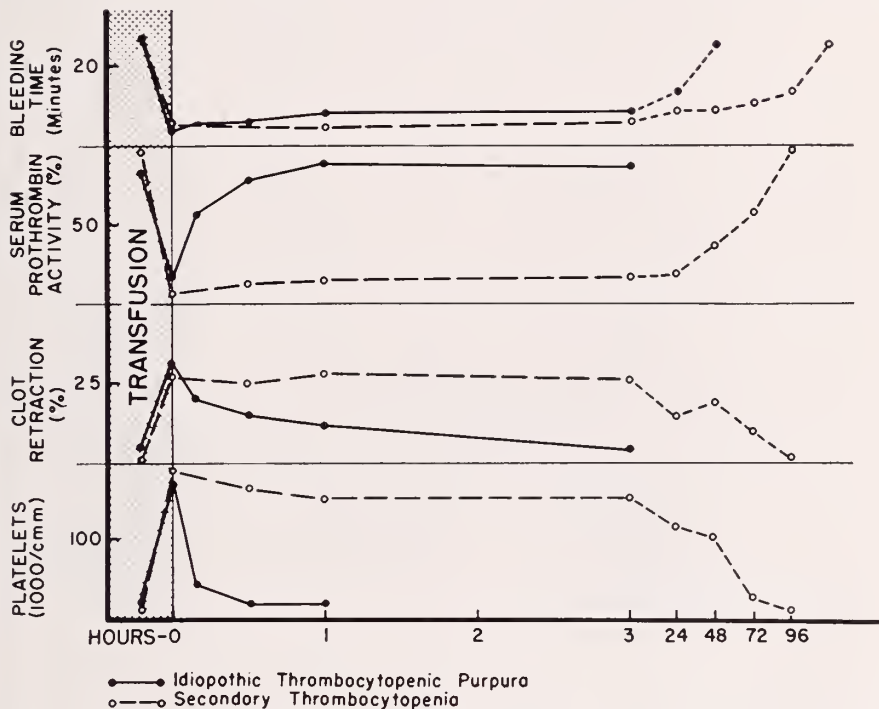


FIG. 1. The effect of the direct transfusion of platelet-rich polycythemic blood on the platelet count, clot retraction, bleeding time and prothrombin activity of serum of patients with idiopathic and secondary thrombocytopenic purpura.*

(c) the destruction of platelets in the peripheral circulation, with or without associated inhibition of their production and release from the megakaryocytes. As you know, one or another of these factors has been advocated to explain the thrombocytopenia of I.T.P., at times with great wealth of clinical and experimental observations. Experiments have been conducted recently by various groups of investigators which permit a better evaluation of some of these possibilities.

We have conducted in our Laboratory direct studies illustrating the role of various organs in the rapid disappearance of injected platelets from the circulation in I.T.P. (Fig. 2) summarizes the results of experiments directed to investi-

* Courtesy of "Blood, the Journal of Hematology," Grune and Stratton Publ., New York.

gate the role of "selective" sequestration and destruction of the platelets by the spleen in I.T.P. Our results are clearly negative. No appreciable difference in platelet count was found in the blood collected directly from the splenic artery and the splenic vein at operation in 12 cases of I.T.P. Moreover, a technique was developed by Dr. Orvar Swenson* for the direct cannulation of the splenic vessels at operation. After injecting large amounts of platelet-rich polycythemic blood or plasma into the peripheral circulation, we failed to detect any significant difference in the platelet count of the blood collected from the splenic artery and the

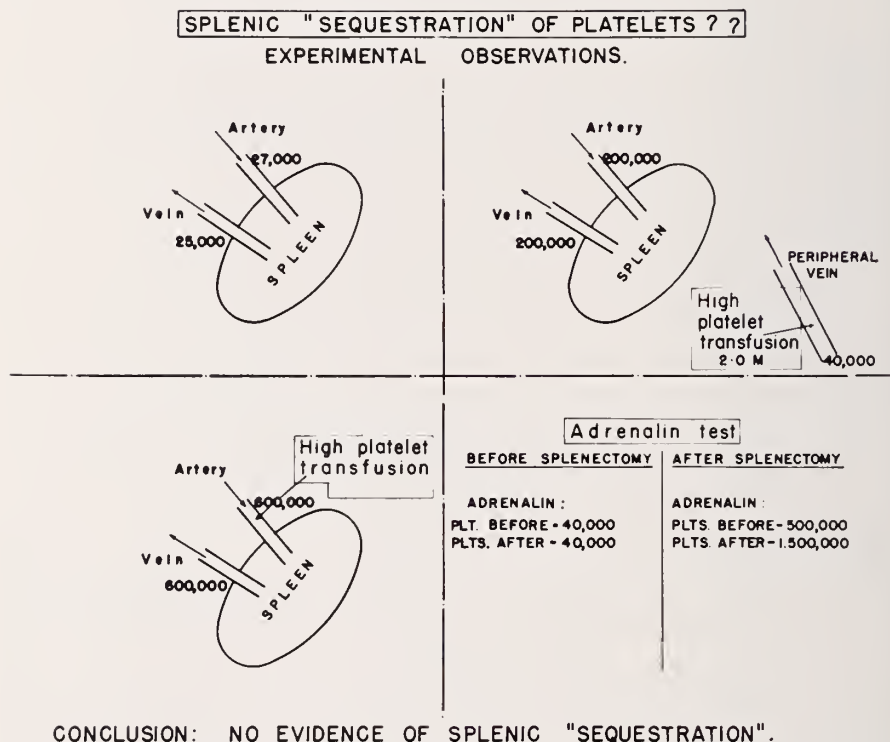


FIG. 2. Failure to demonstrate "selective" sequestration or destruction of platelets by the spleen in idiopathic thrombocytopenic purpura.

splenic vein. When platelet-rich blood or plasma was injected directly into the splenic artery, an almost identical number of platelets could be found in the splenic vein blood. These experiments, as commented upon elsewhere (9), are open to criticism when individually considered. As a body of evidence, however, they all point to the conclusion that there is no evidence of "selective sequestration" of platelets by the spleen in I.T.P. Two additional experiments also favor this conclusion. In several patients with I.T.P., the parenteral administration of adrenalin caused no elevation of platelet count; after splenectomy, however,

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a substantial rise in platelet count followed the injection of the drug (fig. 3). Finally, blood was collected from the splenic pulp within 2 minutes of the ligation of the splenic pedicle. While this blood was more "concentrated" than the peripheral blood, it did not contain an elevated number of platelets in patients with I.T.P. and the difference from the findings in the peripheral blood was well correlated with the difference in red cell count and hematocrit reading. These results again denied the existence of a mechanism of "selective sequestration" of platelets by the spleen in I.T.P. During the course of these experiments evidence was also obtained that the spleen of patients with I.T.P. does not alter the activity of injected normal platelets. Thrombocytes, recovered from the arterial and venous side of the splenic circulation were equally capable, when added to platelet-poor plasma, of restoring to normal the retraction of the clot and the utilization of prothrombin during clotting.

The role of the lung in removing injected platelets in I.T.P. was also investigated. Platelet-rich polycythemic blood or plasma was injected into the antecubital vein in two patients of I.T.P. of the acute variety. After approximately $\frac{1}{10}$ of the calculated blood volume of the recipient had been injected, samples were collected simultaneously from an antecubital vein and a common carotid artery. No significant difference in platelet count could be found in the two samples. The value of this experiment is, of course, limited in view of the fact that a very large volume of blood passes through the lung in a unit of time, as compared to the spleen and repeated passages might be necessary before any evidence of sequestration is obtained. The results, however, indicate that no such sequestration of platelets takes place during a single passage through the lung in patients with I.T.P. Most of the experiments which have been discussed are being repeated with the use of purified platelet preparations now obtained in our Laboratory, and direct transfusions of platelet-rich polycythemic or normal blood and plasma collected and administered with entirely plastic containers and tubes. With the latter technique, which allows complete preservation of platelets during collection and storage for a few days, the results obtained are identical to those observed with the direct "Silicone technique" described above. With the former technique, in which we utilize: (a) Silicone-coated containers and tubing; (b) Sequestrene Na^2 (disodium ethylenediaminetetraacetate dihydrate) solution 1% as anticoagulant and (c) Triton 1339 or Tween 80 as surface active agents to prevent irreversible agglutination of thrombocytes (a method to be reported subsequently and a modification of the procedure of Minor and Burnett, 17) it is possible to obtain discrete suspensions of platelets. These platelets are able "in vitro" to restore to normal the clotting time, clot retraction and utilization of prothrombin during clotting of platelet-poor plasma. When, however, these suspensions are injected in thrombocytopenic patients the rise in platelet count falls much short of the calculated and expected result, although favorable effects on the hemostatic mechanism are clearly achieved. These findings indicate that isolated platelets are more easily destroyed in the circulation.

No results are available at the present time to discuss the role of increased

utilization of platelets at the level of the capillary bed in the pathogenesis of the thrombocytopenia of I.T.P., although we have been impressed by the finding that the rate of platelet disappearance did not improve even when we gave repeated transfusions of platelet-rich polycythemic blood or plasma within a short period of time to a single patient. We must therefore entertain the possibility that platelets in I.T.P. are destroyed directly in the circulation, and that this mechanism

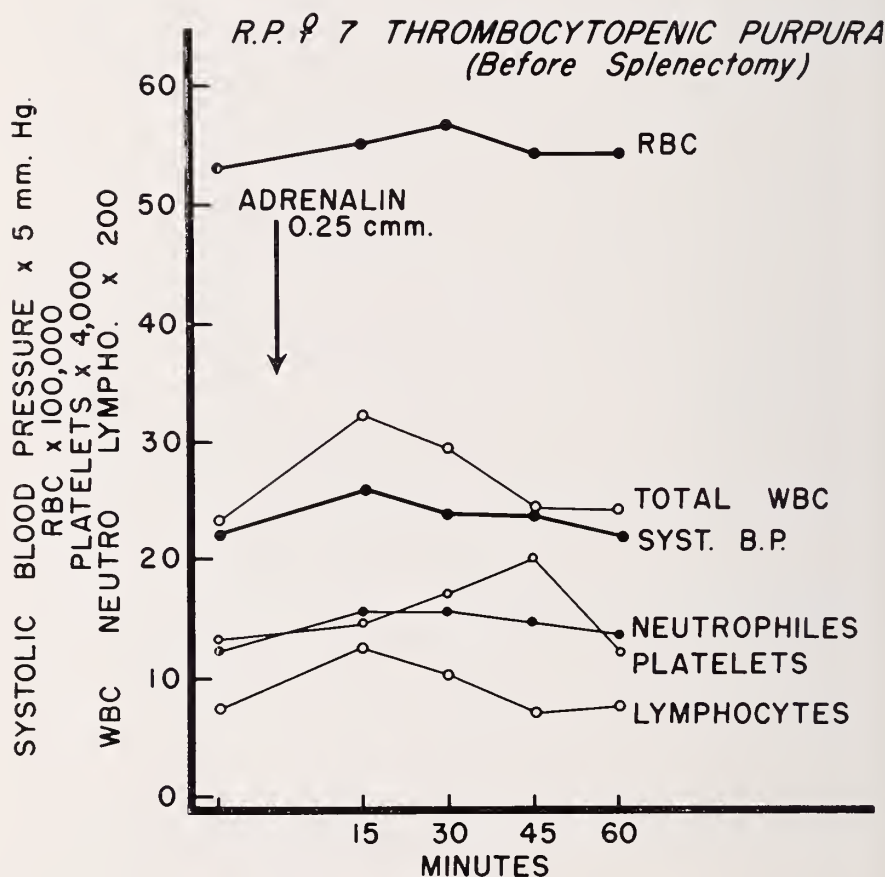


FIG. 3(a)

FIG. 3. Results of an adrenalin test in one case of acute idiopathic thrombocytopenic purpura: (a) before splenectomy; (b) after splenectomy.

might be responsible for the thrombocytopenia and the rapid disappearance of injected platelets. This possibility has been emphasized by a number of investigators and deserves careful analysis. In 1947, Fisher (10) observed cases of associated acquired hemolytic anemia and thrombocytopenic purpura and thought that both conditions could be due to an immune mechanism. This concept has been more recently developed by Evans *et al.* (11). These authors have presented evidence in favor of a common etiology of I.T.P. and acquired hemolytic anemia.

They have rightly pointed out that, in rare instances, the two conditions may occur at the same time (thrombotic thrombocytopenic purpura being, in the writer's opinion, the most striking example of such a possibility); that patients with I.T.P. may present a positive Coombs test, and that sera of these patients may contain substances capable of agglutinating human platelets. We agree with Evans that I.T.P. may be associated with acquired hemolytic anemia and that, in such cases, a positive Coombs test may be found (Table 1). We also agree that

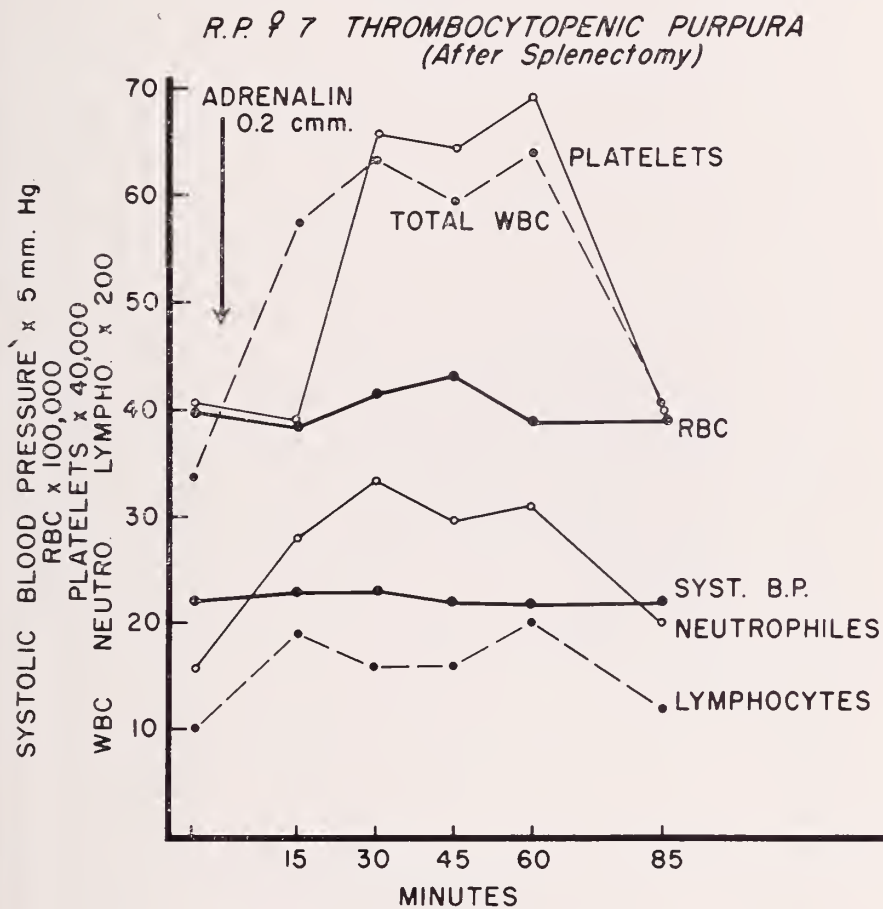


FIG. 3(b)

platelet antibodies may be detected in some cases of I.T.P., but we wish to stress that the demonstration of such antibodies in sera may be fallacious if it is not understood that, on addition of platelets to sera containing prothrombin (like those from patients of I.T.P.) and calcium, thrombin will form and cause a specific agglutination of platelets (12). Results appear to be reliable only after the sera being investigated for platelet agglutinating activity have been decalcified or deprothrombinized, as well as inactivated.

TABLE 1
Laboratory Data on Cases of Idiopathic Thrombocytopenic Purpura

CASE	AGE	SEX	DIAGNOSIS	R.B.C. MILLIONS/CU.MM.	N.B.C. (PER CU.MM.)	PLATELETS (PER CU.MM.)	RETICULO- CYTES	COOMBS TEST	AUTO-AGGLUTININS					
									SALINE			ALBUMIN		
									37°	22°	3°	37°	22°	3°
E.F.	16	F	I.T.P.	3.64	8,100	8,240	2.2	0	0	0	1/2	0	0	1/4
R.A.	5	M	I.T.P.	3.25	9,450	32,500	2.8	0	0	0	0	0	0	0
H.F.	14	M	I.T.P.	4.42	8,650	26,520	1.2	0	0	0	1/4	0	0	1/16
A.P.	5	M	I.T.P.	3.60	10,350	7,200	2.8	0	0	0	0	0	0	0
A.W.	15	M	I.T.P. + A.H.A.	3.75	14,000	13,000	5.2	+	0	0	1/32	1/4	1/2	1/128
R.L.	76	F	I.T.P.	3.40	11,300	13,600	1.1	0	0	0	1/1	0	0	1/2
A.R.	42	F	I.T.P.	2.67	9,100	53,400	1.0	0	0	0	0	0	0	0
D.B.	32	F	I.T.P. + A.H.A.*	3.89	7,300	11,670	1.2	±	0	0	0	0	0	1/2
F.R.	46	F	I.T.P.†	3.97	10,100	138,250	3.4	0	0	0	0	0	0	0
M.Z.	8	M	I.T.P.	5.04	14,050	40,320	3.3	0	0	0	0	0	0	0
T.M.	2	M	I.T.P.	4.18	11,900	20,900	1.5	0	0	0	1/2	0	0	1/1
H.C.	56	M	I.T.P.	4.90	7,700	24,500	0.4	0	0	0	0	0	0	0
J.G.	6	F	I.T.P.	4.10	10,200	6,000	0.2	0	0	0	0	0	0	0
H.C.	6	F	I.T.P.	3.19	14,800	14,000	2.1	0	0	0	0	0	0	1/1
S.C.	22	F	I.T.P.	2.70	21,000	5,000	0.6	0	0	0	0	0	0	0
B.C.	21	F	I.T.P.	4.30	8,950	25,800	0.8	0	0	0	0	0	0	0

I.T.P. = Idiopathic thrombocytopenic purpura.

A.H.A. = Acquired hemolytic anemia.

* in remission, at time of examination.

† chronic variety.

Further evidence has been brought forward that patients with thrombocytopenic purpura may develop a circulating platelet destructive agent. Thus, Aekroyd (13) has shown that the thrombocytopenia of Sedormid purpura is due to a substance present in serum which, in the presence of the drug, can cause lysis of platelets. Moeschlin (14) injected plasma from one such patient into two normal individuals, but failed to induce thrombocytopenia probably because he did not administer Sedormid to the recipients at the same time. Recently, Harrington *et al.* (15) have shown that the plasma of patients with I.T.P. will, when injected into normals, induce persistent (5 to 7 days) thrombocytopenia and, occasionally, cause purpura. The factor, a globulin, persists after the patient has been splenectomized and is depressed by the administration of Cortisone. We have repeated Harrington's experiment in 12 cases to date and find that not all plasmas from patients of I.T.P. contain a demonstrable thrombocytopenic factor. In this respect, patients with I.T.P. may be divided into three groups: (a) those whose plasma causes marked, persistent (5-7 days) thrombocytopenia with clinical purpura (only two such cases have come to our observation); (b) those whose plasma causes moderate thrombocytopenia for 1 to 3 days; and (c) those whose plasma will determine only a moderate, transitory (1 to 3 hours) drop in the platelet count, an effect similar to that consistently observed in normal individuals receiving a transfusion of normal plasma (16). What is the pathogenesis of these various effects remains to be fully investigated, especially in regard to: (a) the influence of the thrombocytopenic factor of I.T.P. on the production of platelets by the megakaryocytes; (b) the intimate mechanism of the induced thrombocytopenia. Studies on these and other obscure aspects have been recently carried out in our Laboratory with the help of a patient of I.T.P. whose plasma and serum contain a strong platelet agglutinin easily demonstrable "in vitro" and very active "in vivo". We shall not present these results for consideration of time and because they are still incomplete. There is no doubt that the new concept that recognizes in I.T.P. an hyperimmune disease and in thrombocytopenia of I.T.P. the indication of the presence of a "humoral factor" directed against the platelets is extremely important and has opened a new hopeful field of investigation. However, with the exception of the rapid disappearance of injected platelets indicating a mechanism of platelet destruction in the disease, no other reported observation or finding is consistently demonstrable in every case of I.T.P. Although the spleen does not appear to have ability to "sequester" platelets selectively and its presence is unrelated to that of the plasma thrombocytopenic factor, the organ has a close connection with the disease that cannot be ignored. How confused the situation is at present is best demonstrated, in our opinion, by the observation that the plasma thrombocytopenic factor, when present, persists even after splenectomy has induced a full clinical and hematological remission in the patient. Therefore, the influence of the spleen on the activity of the circulating thrombocytopenic factor remains to be investigated. As a result of observations in 3 cases of chronic idiopathic thrombocytopenic purpura where platelet agglutinins were demonstrable in the patient's serum and plasma we are brought to believe that, at least in these cases, the mechanism of the thrombocytopenia

may be represented by the removal and destruction by the spleen and other reticulo-endothelial tissues of platelets "sensitized" by attacking agents present in the circulation (? "antibodies"; ? "humors"). This situation would be not unlike that found in some cases of acquired hemolytic anemia. In all of these three patients morphological alterations of the circulating platelets were also clearly detectable, again suggesting that they represented thrombocytes damaged during

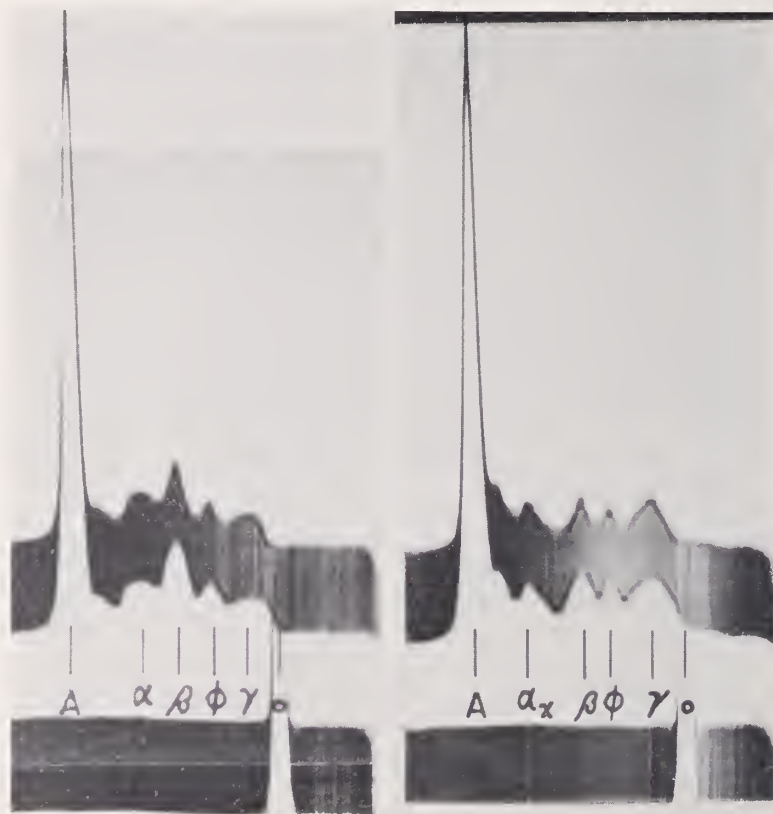


FIG. 4. The characteristic electrophoretic pattern of plasma in acute idiopathic thrombocytopenic purpura. At the left of the reader, normal pattern, at the right, characteristic pattern of acute idiopathic thrombocytopenic purpura†.

their stay in the peripheral circulation. We have also investigated the role of the spleen in the production of antibodies. In one of the patients mentioned, splenectomy has failed to decrease but temporarily the platelet agglutinin titer but after the operation the platelet count has risen from 31,000 to 200,000/cu.mm. This result would indicate, in our opinion, a minor role of the spleen in the production and elaboration of antiplatelet substances but, possibly, a major one in the destruction of "sensitized" platelets. It is difficult, at the present time, to

† Courtesy of the "Proceedings of the Society of Experimental Biology and Medicine," New York, N. Y.

escape the conclusion that I.T.P. is an extremely protean disease, which varies in its clinical manifestations and course and is probably due to widely differing pathogenetic mechanisms (splenic, immunologic, etc.). Whichever the mechanism might be, it finally leads to a double effect: (a) inhibition of platelet formation by the megakaryocytes; (b) increased destruction or utilization of platelets. In relation to the finding of platelet antibodies, it might be of interest that these seem to develop in patients with secondary thrombocytopenia given repeated platelet transfusions. This statement is based on the observation that the rate of disappearance of platelets becomes faster and faster and the administration of platelets is of decreasing usefulness in the control of the bleeding manifestations as they receive an increasing number of transfusions of platelet-rich polycythemic blood. Minor and Burnett (17) have observed a similar phenomenon with the use of their platelet concentrates. In one of these patients a platelet agglutinin (titer $1:32$) actually developed after four platelet transfusions.

To close, I wish to report briefly to you on an observation which might have some significance in relation to the problem of the pathogenesis of I.T.P. We have observed that the plasma of practically every case of acute I.T.P. and only of occasional patients of secondary thrombocytopenia presents a characteristic electrophoretic pattern (18), consisting of: (a) disappearance of the ordinary α_2 and α_3 globulin peaks; (b) their substitution by a faster moving component which has been provisionally defined as α_x (fig. 4). Curiously enough, a similar pattern is also found in hemophilia and, for this reason, it was originally thought that it could be related to the anomaly of the coagulation mechanism (deficient activation of thromboplastin) which is common to the two diseases. This has now been definitely excluded and studies are in progress for the proper interpretation of the anomaly.

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TRANSMESENERIC HERNIA*

REPORT OF A CASE WITH HERNIATION THROUGH THE SIGMOID MESENTERY

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One of the more interesting and rarer forms of internal hernia is transmesenteric hernia. In contrast to the usual concept of hernia wherein the herniating structure is surrounded and enclosed by a mesothelial-lined sac, transmesenteric hernias occur through defects or holes in the mesentery, from one area of the peritoneal cavity to another and are devoid of a sac. In addition to the most common sites of occurrence, namely the small bowel mesentery and mesocolon, all broad, flat-shaped structures within the abdomen may present apertures through which other abdominal viscera may herniate. Thus, there are recorded instances of hernia through such structures as the broad ligament (10, 20, 25), the greater omentum (1), and the falciform ligament of the liver (7).

The majority of authors restrict the use of the term transmesenteric hernia to those through the mesentery of the terminal ileum, through the so-called Treves's field. Others have included the mesocolon, and still others hernias through the gastric "ligaments", the gastro-colic and gastro-hepatic ligaments. Hansmann and Morton (12) went so far as to group these cases as mesenteric, paracecal, ileo-appendicular, ileocolic and ascending mesocolic in addition to those cases through the transverse mesocolon, greater omentum and a miscellaneous group that included the broad and falciform ligaments. Since from anatomic-pathologic considerations the etiology of practically all of these defects through the structures named is similar, and since in addition the clinical course and treatment are similar, we believe that the term transmesenteric hernia should be more encompassing. We feel that it should include all internal herniations of a viscus or portion thereof through a defect in one of the several broad, flat supporting membranes within the peritoneal cavity.

The small bowel mesentery, particularly at the terminal ileum, is the most frequent site of transmesenteric hernia (6, 14, 17, 24, 30). Dalton (5) in 1944, was able to collect 76 cases, Turel (29) 31 cases and Cutler and Scott (4) 35 cases. Defects have been described both at the root (2, 8, 11, 27) and near the center (16, 19) of the mesentery. Cutler and Scott also describe 6 instances of defects at the mid-ileum and 2 in the jejunal mesentery.

Hernias through the transverse mesocolon represent the most frequent of the entire mesocolon with 60 cases collected by Hansmann and Morton. In addition these authors collected 4 cases with hernia through the ascending mesocolon, including one of their own. The inclusion of these latter cases as transmesenteric herniae is open to question since the defects in the "mesentery" are more truly

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defects in the medial and lateral peritoneal reflections rather than through a dependent mesenteric structure. The illustrations accompanying their case as well as those with Cullen's case (2) would seem to bear that out.

The only heretofore described case of herniation through the sigmoid mesentery is that of Turel (29), although a case of Hohlbaum (14) has been erroneously quoted as being similar. The latter article was abstracted from the German by Heller (13). Closer analysis of the original description and the corresponding illustration reveals that the defect was in the mesentery of the terminal ileum and that the sigmoid colon was merely the viscus incarcerated in the defect.

Turel's patient was a 39 year old woman who developed acute intestinal obstruction. There was no history of previous abdominal disease or injury. At laparotomy the small bowel was collapsed but large bowel obstruction was present. "The cause of the obstruction was found to be due to a hole in the mesosigmoid through which a small loop of the sigmoid colon had prolapsed and was strangulated. The hole was between 3 and 4 inches long, extending from the attachment of the mesosigmoid to the mesenteric border of the bowel. The edges were smooth, rounded and thickened. It was undoubtedly of long standing and possibly congenital in origin". It was possible to reduce the incarceration and repair the defect. The patient made an uneventful convalescence.

We have recently encountered another case of herniation through a defect in the mesosigmoid. The rarity of the condition and the classical clinical picture presented prompt this report.

CASE REPORT

History: The patient, Mr. W. B., MSH #611734, was an 80 year old white man who experienced a sudden onset of nausea, vomiting and generalized abdominal pain 30 hours prior to his admission. Vomiting persisted unremittingly to the time of admission. The pain was constant, localizing in both lower quadrants shortly before admission. He had taken nothing by mouth for 24 hours, and had had a normal bowel movement before the onset of the present illness, but none since. There was no history of change in bowel habits, no melena and no weight loss.

System review revealed that the patient was a known cardiac of many years duration. He had been fibrillating for 12 years and was taking $1\frac{1}{2}$ grains of digitalis daily. In addition he had intermittent orthopnea, dyspnea and ankle edema.

The only previous surgical procedure had been a right inguinal herniorrhaphy.

Examination: Temperature, 101.6° F. Radial Pulse was 90 and grossly irregular with a blood pressure of 150 systolic and 68 diastolic. He was a well developed, well nourished white male, appearing acutely ill. He vomited several times during the examination, the vomitus being fecal in character. The lungs were clear to percussion and auscultation. Examination of the heart revealed a typical auricular fibrillation with a pulse deficit of 30. There was a harsh precordial systolic murmur loudest over the mitral and aortic regions. The abdomen was slightly distended and diffusely tender, more marked however, in the right lower quadrant. No masses were palpable and there were no audible peristaltic sounds. There was a large left inguinal hernia, readily reducible. Rectal examination revealed a prostate 3 times its normal size and a normal appearing stool that gave a faint trace of a positive guaiac test.

Laboratory Data: White blood count, 22,500 with 98 per cent of polymorphonuclear leucocytes and 2 per cent of lymphocytes. Urine: albumen, 0; sugar, 0; acetone, 0.

Course: The admission diagnosis was acute gangrenous appendicitis with perforation

and peritonitis. However, because of the history of long standing auricular fibrillation it was also felt that mesenteric thrombosis was a likely possibility. The patient was rapidly prepared and taken to the operating room for exploration. Preparatory to giving anesthesia, his blood pressure was found to have fallen from the admission pressure of 150/68 to 80/60 and that the pulse was extremely thready. Because of this sudden change it was felt that the patient would not survive surgery and it was decided to postpone operation until the patient had demonstrated some signs of improvement. He was returned to his room where supportive therapy was instituted. He became increasingly confused and disoriented, suddenly becoming dyspneic and expired $4\frac{1}{2}$ hours after admission.

Post-Mortem Findings (§14647): There was approximately 1500 cc of red-black bloody free fluid distributed throughout the abdominal cavity. Presenting in the mid-lower abdomen were 3 large loops of purple-black, thick-walled small bowel, identified as ileum. These



FIG. 1. Post-mortem specimen. The gangrenous loops of ileum are to the right of the sigmoid in the photograph. Reduction of several inches of gangrenous bowel took place during removal of the organs. The probe is placed through the sigmoid defect.

loops of ileum were found to represent strangulated herniations through a circular defect in the mesosigmoid. The gangrenous bowel lay to the left of the medially displaced mesosigmoid with afferent and efferent loops lying to the right of the mesosigmoid (fig. 1). The proximal jejunum and ileum were dilated, thin walled and dusky bluish in the few centimeters before entering the hernia, but with a smooth glistening serosa. The distal ileum, 85 cm. (33 inches) in length to the ileocecal junction, was collapsed and normal in color and caliber.

The strangulated segment of ileum, 130 cm. in length, was moderately dilated. The wall of the bowel was thick and edematous, friable and the serosa presented a surface dulled by a fine fibrinous exudate gently binding the loops together. The mucosa was edematous, hemorrhagic and very friable. The liquid bowel contents were bloody. At either end of this segment of bowel there was a compression groove in the serosal aspect marking the limits of the infarction and corresponding to the points of pressure by the defect in the mesentery. The incarcerated mesentery to this segment of bowel was thick, edematous and ecchymotic. 15 cm. proximal to the point of exit of the incarcerated bowel an incidental finding was a Meckel's diverticulum. The diverticulum was 7.5 cm. long, with a wide neck and a dependent bulbous portion. When opened the neck was 3.5 cm. in circumference, the

bulbous portion 7.0 cm. in circumference. It presented gross characteristics identical with the remainder of the incarcerated ileum. Microscopically, there was complete necrosis of all layers of the bowel wall.

The hole in the mesosigmoid was roughly oval, 1.7 cm. in greatest diameter and located within 3.5 cm. of the bowel wall (fig. 2). The rim of the defect was smooth, only slightly thickened by fibrous tissue strands at one border but there was no undue fibrosis in the remainder of the rim of the defect or the adjoining areas of the mesosigmoid. Microscopically, minimal simple fibrosis and areolar tissue were seen.

The sigmoid colon and the remainder of the large bowel were not remarkable except for multiple small diverticuli varying up to 1.0 cm. in length. There was no evidence of diverticulitis.

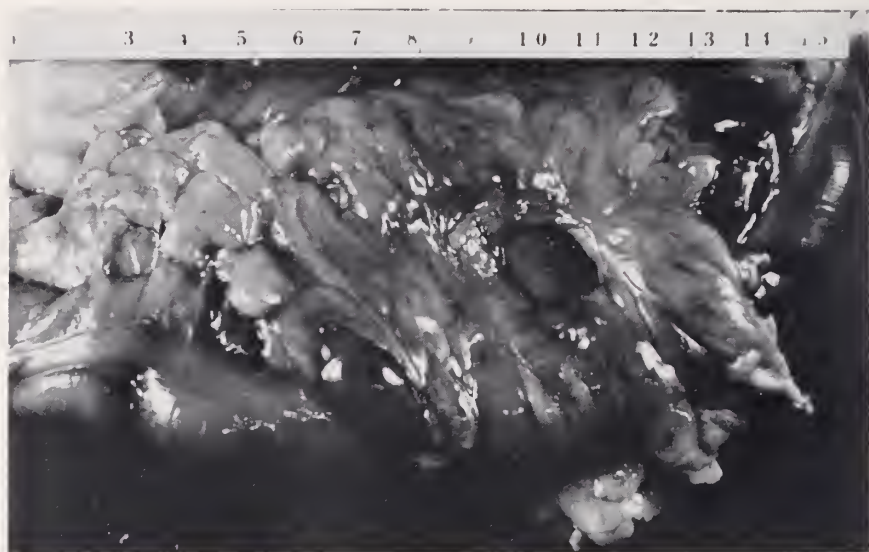


FIG. 2. Mesosigmoid showing the roughly oval defect

Other findings of the autopsy included cardiac hypertrophy, an accessory right coronary ostium and artery, moderate bilateral pulmonary edema, cholelithiasis, a small adrenal cortical adenoma, multiple small renal cortical cysts and a microscopic occult carcinoma of the prostate.

DISCUSSION

Incidence: In 1939 Hansmann and Morton (12) reviewed 467 cases of internal hernia of which 99 or 21% were found in the small bowel mesentery, 60 (13%) were in the transverse mesocolon and 4 (1.0%) in the ascending colon. In a study of 335 cases of intestinal obstruction, McIver (21) found 3 (0.9%) due to internal hernia, while Gibson (9), in a similar study of 1000 cases of obstruction, found that 34 or 3.5% were due to transmesenteric hernias.

Transmesenteric hernias have been described in all age groups, from as early as 4 days of age through the eighth decade. The sex distribution is approximately equal.

The incidence of mesenteric defects is recorded in only two anatomic studies. Mitchell (24) found genuine mesenteric defects 3 times in over 1600 autopsies.

Each was found in the mesentery of the terminal ileum and each was devoid of a herniation at the time of examination. Meade (23) found two mesenteric defects in an examination of 50 dissecting room cadavers.

The holes are almost invariably solitary, although Treves (28) describes a case of a 52 year old male with an avascular patch in the mesentery of the ileum, the patch being represented by a cribriform plate containing 20 discrete holes. Although the defect in Turel's (29) case was between 3 and 4 inches long, for the most part they are considerably smaller, ranging from 1 to 3 cm. in diameter and roughly oval or circular in shape.

Etiology: Although trauma and inflammation have been held by some to be the cause of some mesenteric holes, the consensus of opinion of most writers tends to support a congenital etiology. Wilms (31) divided these defects into acquired and congenital types, referring the acquired type to 3 causes: (a) abdominal injuries by direct violence (b) inflammation followed by contraction and dragging, and (c) operations such as intestinal resection or removal of tumors from the mesentery. In a review of 26 cases by Cutler (3), a history of trauma was elicited in 7. Johnson (15) cites Braun's case operated on 3 days after a fall and in which the mesenteric hole was slit-like and with rough edges resembling a laceration. Mitchell's patient (24) sustained a fall down a flight of stairs, striking the abdomen two days prior to the onset of his illness. At operation, a hernia through the ileal mesentery was found and the edges of hole were described as smooth. The vast majority of cases fail to reveal, however, a history of trauma and it rarely can be incriminated as a factor.

Inflammation is similarly lightly held in importance. Prutz (26), Hohlbaum (14) and King (17) strongly supported the inflammatory theory. King believed that inflammation, leading to thrombosis of vessels, fibrosis and atrophy of the mesentery ultimately led to the formation of the defect and reported one case of appendicitis in which this sequence seemed to be demonstrated. Hohlbaum's first case presented adhesions in the vicinity of the defect and a calcified mesenteric lymph gland was lodged in the opening. However, as Cutler points out, the fact that such defects are not found more commonly after peritonitis "renders it improbable that the inflammation is an important factor in most cases. If it were, defective mesentery would be more frequent after appendicitis. On the other hand, such inflammatory changes may result secondarily because of the defect".

Greatest support is given to the developmental or congenital theory and is based principally on the early observations of Treves (28). In the foetus he had observed "that the ileo-colic branch of the superior mesenteric artery circumscribes, by its anastomosis with the last of the intestinal arteries, an area on the mesentery, of a well rounded or oval shape. This area is remarkable, in so far that it presents no fat, no visible blood vessels of any kind, even in well injected specimens, and is never occupied by any mesenteric glands. In many bodies beyond the period of foetal life, I have met with this singular and isolated area in the mesentery still retaining the characters just described, and rendered conspicuous by its thinness and bloodlessness. It will be seen that this area has the

precise situation, the outline, and the dimensions of the mysterious mesenteric hole; and by the atrophy of the peritoneum occupying the district such a hole could be formed". It is interesting to note that Wilms (31) quoted Loebel, who in 1844 reported a case with a defect in the mesocolon and explained its existence on similar grounds. Treves's observations are further supported by Macklin's (18) work whose studies on the development of the pulmonary alveolar spaces revealed that coalescence and development of a defect takes place when two epithelial layers are opposed in the presence of a deficient intervening supporting stroma of connective tissue.

Although the majority of mesenteric defects occur in the region of the distal ileum, the above observations give a ready explanation for the formation of defects elsewhere in the mesentery and mesocolon. The infrequent history of trauma and the almost invariable absence of adhesions as a manifestation of inflammation serve further to reinforce the congenital theory.

Clinical Manifestations: The sudden onset of acute intestinal obstruction is most frequently the first indication of the condition. The usual symptoms of obstruction are present in varying degrees of severity, namely, abdominal pain, nausea, vomiting, and obstipation. The signs that may be present depend in large part on the duration of the incarceration and obstruction, as well as the state of viability of the involved bowel. The structure most frequently found herniated is the small bowel and the signs are those of a small bowel obstruction. The abdomen is tense, tender and tympanitic. Peristaltic sounds are usually hyperactive with frequent rushes and tinkles. Tenderness and rebound localized in one area of the abdomen associated with leucocytosis and temperature elevation frequently portend compromise of the bowel blood supply and even gangrene. Roentgenographs usually serve to confirm the clinical impression. Cullen's case (2) is of unusual interest in that it presented both small and large bowel obstruction. A 2 cm. circular defect was found in the mesentery of the ascending colon through which a loop of descending colon and sigmoid had passed, producing large bowel obstruction. In passing from left to right the colon had passed anteriorly to the ileum and its mesentery. Obstruction and distention of the left colon was sufficient to obliterate the blood supply of the ileum producing gangrene of 5 feet of ileum and small bowel obstruction.

The diagnosis of transmesenteric hernia is rarely made pre-operatively. The absence of the more frequent causes of obstruction, as external hernia or previous surgery with subsequent adhesion and band formation, should arouse a high degree of suspicion toward one of the more obscure conditions including internal hernia. When present, a history of trauma is of great value. A not infrequent and most valuable finding is the history of previous episodes of recurrent abdominal pain with or without obstruction. Cutler's first review of 26 cases (3) revealed 6 cases with a history of previous attacks of abdominal pain. He added his own case of a 9 year old girl who had had an episode of abdominal pain of 24 hours duration 6 weeks prior to surgery. He subsequently reported an almost identical case (4) in a 6½ year old boy whose first episode occurred 8 months prior to admission. The case of Hansmann and Morton (12) gave a history of recurrent cramps for several months and increase in the girth of the upper abdomen.

Johnson's (15) second case had been hospitalized twice within 12 days for abdominal pain and vomiting, each episode subsiding spontaneously, after a vigorous exertion of vomiting. A provisional diagnosis of recurrent strangulation of an internal hernia was made; at laparotomy an empty intersigmoid hernial sac was found, the orifice of which was large enough to permit spontaneous reduction of the hernia.

Finally the use of the X-ray should be cited as an aid in diagnosis. In the non-emergent patient, or the patient in an interval stage, the judicious use of barium by mouth or by enema may reveal abnormal locations of bowel, either in the location per se or in relation to other segments of bowel, and thereby suggest internal hernia. Similarly the disposition of loops of bowel may be suggested on plain flat films, utilizing antero-posterior, lateral and erect positions, and particularly when agents as the Levine and Miller-Abbott tubes are indwelling. In the case of Hansmann and Morton the diagnosis of internal hernia was suggested because of evidence of small bowel behind the stomach and colon. At operation a defect of the lateral peritoneal leaf of the ascending colon was found and into which 138 cm. of terminal ileum had herniated and extended retroperitoneally behind the colon and stomach.

Treatment for the most part is of the emergency nature. The diagnosis of unremitting mechanical obstruction makes laparotomy mandatory. In the presence of viable bowel, the hernia should be reduced, enlarging the usually tight and restricting orifice and then completely closing the defect in the mesentery. If the bowel is gangrenous, resection and anastomosis must be carried out although Cutler and Scott (4) are of the opinion that the Mikulicz type of resection offers the patient the optimum chance for survival.

The mortality in transmesenteric hernia is high, varying from 15% to 50%, and due principally to the high frequency of gangrenous bowel encountered. Cutler and Scott report an incidence of gangrene of 62% (31 cases) in their surgery of 50 cases (4). Prompt diagnosis and early surgery, coupled with judicious utilization of the vast array of modern adjuvants to surgery, including the antibiotics, should substantially reduce the previously reported high mortality rates.

SUMMARY

The subject of transmesenteric hernia is reviewed from the standpoint of etiology, incidence, diagnosis and clinical manifestations. It is suggested that the term transmesenteric hernia be broadened to include all internal herniations through a defect in any of the several broad, flat supporting membranes within the peritoneal cavity.

A case of internal herniation through a defect in the sigmoid mesentery is presented. We have been able to find only one other similar case recorded in the literature.

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SARCOIDOSIS WITH BRONCHIAL INVOLVEMENT*

A REPORT OF TWO CASES WITH BRONCHOSCOPIC BIOPSIES

LOUIS E. SILTZBACH, M.D. AND MAX L. SOM, M.D.

In the voluminous literature relating to sarcoidosis, scant reference is made to lesions in the bronchi. This report concerns two patients whose symptoms suggested bronchial obstruction on the basis of broncholithiasis and neoplasm, respectively. The microscopic findings of sarcoid lesions in biopsies of the bronchial wall came as a surprise.

CASE REPORTS

Case 1: J. W., a 40-year-old white subway attendant, was admitted to the Mount Sinai Hospital on March 2, 1951. His illness began one year previously with non-productive cough and occasional wheezing respiration. Two months before admission, he became acutely ill with severe cough, persistent fever, night sweats and loss of weight. He expectorated large quantities of purulent sputum.

Examination: On admission the patient appeared to be acutely ill. Temperature was 101.6°F., pulse 100, and respiration 34 per minute. The lips and nail beds were moderately cyanotic. Diminished breath sounds with prolonged expiratory phase and coarse, moist rales were heard over the lower portions of the anterior and posterior surfaces of the right chest. The lymph nodes in the posterior cervical triangles and the inguinal regions were slightly enlarged. The spleen edge was felt three fingerbreadths below the left costal margin.

Laboratory Findings: The blood count was within normal range except for a slight shift to the left. The erythrocyte sedimentation rate was 40 mm. after one hour (Westergren). The urine showed no abnormality. Blood cultures were sterile and the sternal marrow had a normal appearance. There was no serologic evidence of syphilis or brucellosis. Acid-fast bacilli were absent in the sputum. Sputum cultures yielded a normal flora. No carcinoma cells could be identified in stained sputum smears.

A chest roentgenogram showed shrinkage and consolidation of the right middle lobe. There were also faint linear and nodular densities scattered throughout both lung fields and the left hilar shadow was prominent (fig. 1a).

Bronchoscopy was performed on March 8, 1951. From the orifice of the right middle lobe bronchus, there was a copious flow of non-odorous pus which welled up into the right main bronchus. The secretions recurred profusely, preventing a clear view of the bronchial mucosa. The rest of the bronchial tree appeared to be normal, and biopsy was not performed.

The clinical impression was that the patient had suppurative pneumonia with bronchiectasis of the right middle lobe. Bronchostenosis, secondary to broncholithiasis was thought to be the underlying cause of the pulmonary infection. The splenomegaly remained unexplained.

Course: Penicillin was administered intramuscularly in a daily dosage of 300,000 units for the first two weeks with little benefit. Chloromycetin 2 grams, Streptomycin 1 gram and Gantrisin 3 grams daily were added without remarkable response.

Fever and wheezing persisted, the sputum remained purulent and measured up to 100 cc. daily, and the patient's weight continued to decline. Intratracheal instillations of a mixture of Penicillin and Streptomycin reduced the daily sputum volume to 30 cc. but there was no

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change in the patient's general condition or in the roentgenographic appearance of the lungs.

Bronchoscopy was repeated during the fourth week. Abnormal findings were limited to the bronchus of the right middle lobe. Secretions from its orifice had lessened and now the bronchus could be inspected thoroughly. The mucosa was granular and thickened, causing considerable narrowing of the lumen. With the aid of a dilator, the medial and lateral branches of the bronchus were visualized and these were found to be patent. A specimen of the wall of the middle lobe bronchus was obtained by biopsy.

Microscopic sections showed that the submucosa of the bronchial wall was infiltrated with non-caseating, epithelioid-cell tuberculoid granulomata. Inflammatory cells surrounded the tubercles (fig. 2a). Stains for acid-fast bacilli were negative. The appearance of

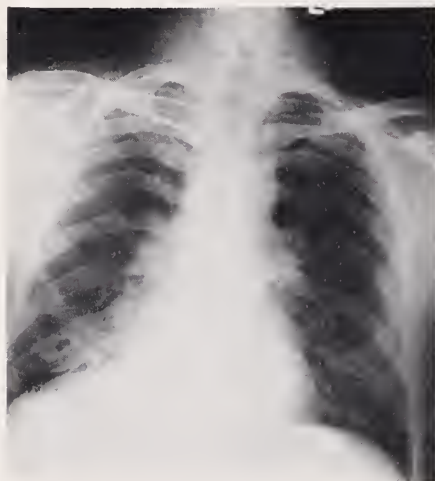


FIG. 1a



FIG. 1b

FIG. 1a. (Case 1)—Roentgenogram of chest on patient's admission shows consolidation and shrinkage of the right middle lobe and some prominence of the left hilar density. Faint nodular and linear densities in both lung fields are not visible in reproduction.

FIG. 1b. X-ray of chest of same patient after five weeks' treatment with Cortisone shows clearing of right middle lobe consolidation leaving residual streaking.

the granuloma was consistent with that which is found in sarcoidosis. Bronchoscope biopsy was repeated one week later with the same microscopic findings. A bronchogram disclosed cylindrical bronchiectasis of the bronchi of the right middle lobe.

With the finding of the granulomatous lesions in the bronchial wall, further investigations were carried out and they confirmed the diagnosis of sarcoidosis. The tuberculin test was negative in a dilution of 1:100 O.T. (Coccidioidin and Histoplasmin intradermal tests were also negative.) The serum albumin was 4.2 Gm. and the globulin was 3.8 Gm. per 100 cc. The axillary lymph nodes had enlarged slowly during the patient's hospital stay and one of these was excised. Microscopically, the lymph node substance was found to be studded with the characteristic non-caseating, tuberculoid granulomata of sarcoidosis (fig. 2b). Acid-fast stains of the sections failed to reveal any organisms. The Nickerson-Kveim intradermal test was positive, grossly and microscopically. Slit-lamp examination revealed a quiescent uveitis of the right eye.

A chest roentgenogram made at the onset of the patient's complaints one year previously was obtained, and this revealed fine, nodular seeding and linear streaking throughout both lung fields. There was considerable enlargement of the lymph nodes in both hilar areas. There was, however, no evidence of consolidation and shrinkage of the right middle lobe.

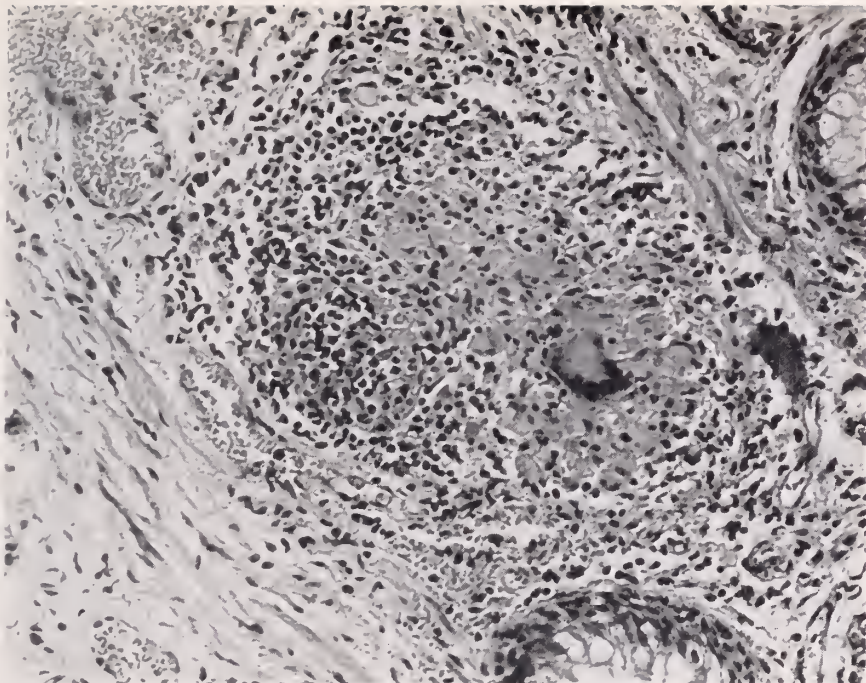


FIG. 2a. (Case 1)—Photomicrograph of a section of bronchial wall obtained by bronchoscopic biopsy shows an epithelioid-cell granuloma with a giant cell situated in the submucosa amid bronchial glands. ($\times 230$)

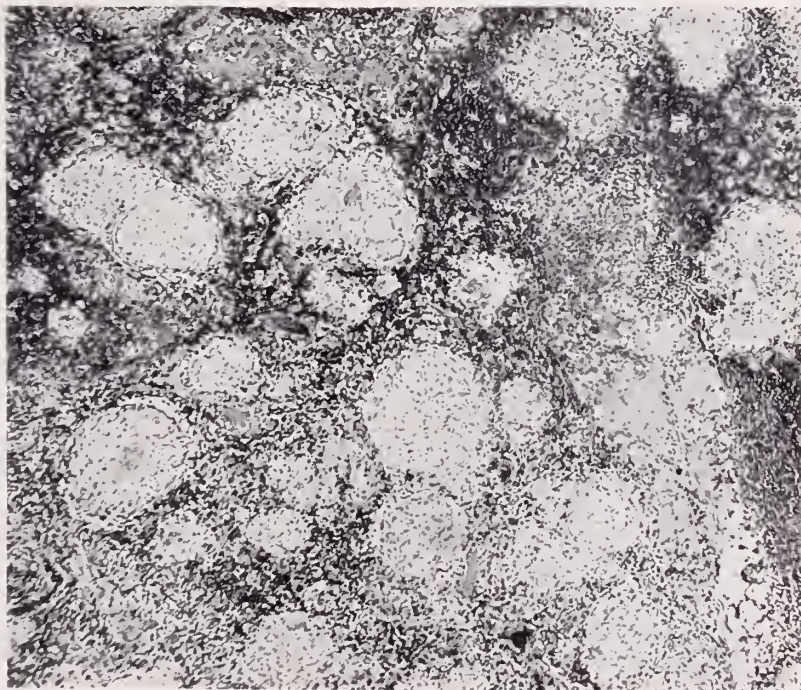


FIG. 2b. Photomicrograph of a section of an axillary lymph node shows large, bland, epithelioid-cell granulomata studding the lymphoid substance. ($\times 87$)

A comparison with the hospital films showed that the hilar lymph node enlargement had almost completely regressed, but the parenchymal lesions had persisted.

It was therefore apparent that the patient was suffering from generalized sarcoidosis involving peripheral and mediastinal lymph nodes, lungs, bronchial wall, spleen and uveal tract of the right eye. In view of the patient's indifferent response to a six-weeks' course of combined antibiotic therapy, a right middle lobe excision was considered. It was feared, however, that the rigidity of the bronchial wall involved by sarcoidosis might prevent healing of the bronchial stump and lead to a bronchopleural fistula. Since the effects of Cortisone on sarcoidosis were being studied, this patient was included in the series. Cortisone therapy was undertaken in spite of the danger of spreading the bronchopulmonary infection. It was felt that the risk was less than that which would be involved in lobectomy. To minimize it, antibiotics were continued while the Cortisone was being given, and no spread of infection occurred.

Cortisone Therapy: Details of the Cortisone therapy and the patient's response have been reported elsewhere (1). Here it may be stated that there was prompt subsidence of fever, sharp reduction of the daily sputum volume, a fall in the E.S.R. and gradual shrinkage of the enlarged peripheral lymph nodes.

Bronchoscropy after three weeks' Cortisone therapy revealed a widely patent orifice to the right middle lobe. A chest roentgenogram made after five weeks showed marked clearing of the right middle lobe consolidation, leaving residual streaking. The nodular and linear densities in the rest of the lung fields were no longer clearly visible but the left hilar density remained prominent (fig. 1b).

Cortisone therapy extended over a period of sixty-three days and was followed by administration of Corticotropin for a like period in diminishing dosage. Throughout treatment, the patient had no complaints and gained weight and there was no recurrence of respiratory symptoms. Repetition of the bronchoscropy on the sixtieth day of therapy showed a normal-looking mucosa in the bronchus to the right middle lobe. Yet, tissue removed by biopsy still showed a residual tubercle. The patient has been observed for four months following therapy. He has resumed his work and feels well. Some moist rales are still heard over the right middle lobe area and the chest roentgenogram shows residual streaking in that region.

Comment: This is a case of generalized sarcoidosis with involvement of the bronchus to the right middle lobe. It is of interest that the acute symptoms of the illness were caused by pulmonary suppuration behind a granulomatous narrowing of the lumen of this bronchus. Since the most common cause of right middle lobe suppuration and shrinkage is broncholithiasis, it was first supposed that this condition was at the root of the patient's difficulty. However, the presence of epithelioid-cell tubercles in tissue removed by bronchoscopic biopsy promptly led to a proper interpretation of other seemingly disparate findings, and the generalized nature of the disease process was uncovered.

Case 2: H. O., a 35-year-old housewife, came under observation in June 1946 because of respiratory complaints of one year's duration. She complained of cough, dyspnea, wheezing respiration and stridor of increasing severity. Initially, she had been studied by an allergist who could not find any significant sensitizing agent.

Examination: The patient was a well-nourished woman whose respiration was somewhat labored and noisy. The nose, pharynx and larynx had a normal appearance. Breath sounds over both chests had a prolonged expiratory phase. There were numerous sibilant and sonorous rales. Slightly enlarged lymph nodes were present in the left axilla. No abdominal masses were felt. There was no ankle edema.

Laboratory Findings: The blood count was within normal range. The tuberculin test was negative in a dilution of 1:100 of O.T. The sputum contained no acid-fast bacilli. An electro-



FIG. 3a



FIG. 3b

FIG. 3a. (Case 2)—Roentgenogram of chest dated December, 1945 shows marked enlargement of the hilar and right paratracheal lymph nodes with some streaking in the mesial portion of the right lower lung field.

FIG. 3b. Film dated January, 1948 shows disappearance of the enlarged lymph nodes. Except for some residual streaking in the region of both lung roots, the lung fields have a normal appearance.



FIG. 4a

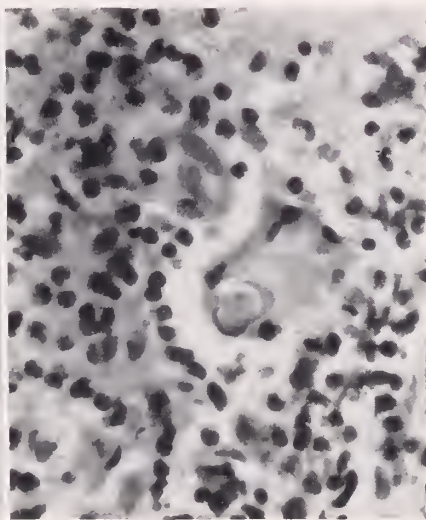


FIG. 4b

FIG. 4a. (Case 2)—Photomicrograph of a section of bronchial wall obtained by bronchoscopic biopsy shows the surface epithelium little disturbed but the submucosa is infiltrated with non-caseating epithelioid-cell tubercles containing giant cells. ($\times 160$)

FIG. 4b. Higher magnification of the same section of bronchial wall shows a giant cell with a concentrically lamellated concretion; i.e., a so-called Schaumann body. ($\times 480$)

cardiogram showed no abnormality. A chest roentgenogram had been made in December 1945. This showed enlargement of the lymph nodes in both hilar areas and in the right paratracheal region. Some linear densities were present in the mesial portion of the lower lung field on the right side (fig. 3a).

Course: No diagnosis had been established after one year of observation. The patient's

respiratory symptoms were becoming progressively more disabling and it was suspected that there might be a bronchiogenic carcinoma with mediastinal node metastases. She was therefore referred for bronchoscopy to one of us (M.L.S.) and this was performed on June 19, 1946. The trachea had a normal appearance. There was some narrowing of the right stem bronchus above the level of the middle lobe bronchial orifice. The left main bronchus was also narrowed but to a lesser extent. The narrowing in both instances appeared to be the result of external pressure; the mucosa appeared normal. In the middle lobe bronchus, however, the mucosa was considerably thickened, leading to virtual occlusion of this bronchus. A 9 mm. bronchoscope could not be passed into the lumen. There was no ulceration of the mucosa nor were there any gross signs of infection. A deep biopsy of mucosa and submucosa was performed.

Microscopic studies showed that the surface mucosa was thin and intact. In the submucosa, at all levels, there were numerous non-caseating, epithelioid-cell tuberculoid granulomata containing many giant cells of the Langhans type (fig. 4a). Within a few giant cells concentrically lamellated concretions were present, (Schaumann bodies) (Fig. 4b). Acid-fast bacilli were not found in stained sections.

Without any therapy, the cough, wheezing and stridor slowly subsided. Permission for biopsy of an axillary node was refused. In November 1946, a chest roentgenogram disclosed some shrinkage of the enlarged mediastinal nodes, and in January 1948, the appearance of the lung fields was normal except for some residual streaking at both lung roots. (fig. 3b). When last examined in November 1951, the patient was attending to her household duties and she had had no recurrence of symptoms.

Comment: This patient had enlarged mediastinal and left axillary lymph nodes, linear streaking in the lung fields and a negative tuberculin test. Tissue obtained by bronchoscopic biopsy showed a granuloma characteristically found in sarcoidosis. The spontaneous regression of the hilar lymphadenopathy over an eighteen-month period corresponds to the usual course of such nodes in the remissive phase of sarcoidosis.

DISCUSSION

Sarcoidosis involving nasal, pharyngeal, laryngeal and tracheal mucous membranes has been described in many reports. These have been fully summarized in a recent paper by Lindsay and Perlman (2). There have been only four individual case-reports of bronchial wall involvement confirmed by bronchoscopic biopsy and one report of this finding at necropsy.

Benedict and Castleman (3) described a case in 1941. This concerned a 20 year old woman with generalized sarcoidosis who complained of cough, expectoration and wheezing respiration. The mediastinal nodes were enlarged but there were no evident pulmonary lesions. Bronchoscopy revealed numerous 2-3 mm., bleb-like nodules in both main bronchi whose lumina were narrowed. Tissue removed by biopsy showed typical non-caseating epithelioid-cell tubercles with giant cells. The patient's condition improved during the following six months.

Olsen (4) reported a case in which the only tissue confirmation of the diagnosis of sarcoidosis came from a bronchoscopic biopsy—as in case 2 of the present report. The patient was a 47 year old man who had cough, hoarseness and dysphagia. Chest roentgenogram showed a right upper lobe infiltration with enlargement of hilar nodes bilaterally. The tuberculin test was negative. On bronchoscopy, the lateral wall of the right main bronchus had a faintly nodular

appearance. Tissue removed by biopsy showed epithelioid-cell tuberculoid granulomata surrounded by lymphocytes. There was no caseation. The patient's condition improved spontaneously.

Jacob (5) performed a bronchoscopy on a patient with generalized sarcoidosis who complained of cough and mild dyspnea. The lungs were studded with miliary nodules and the hilar nodes were enlarged bilaterally. He found the left main bronchus somewhat narrowed by external compression. In the right main bronchus there were several faintly hemorrhagic flat areas measuring 2-3 mm. in diameter. Biopsy of these nodules was carried out and microscopically, non-caseating tubercles with many giant cells were found in the submucosa of the bronchial wall. The patient's condition improved and the hilar nodes regressed.

Harvier et al. (6) observed a 34 year old woman with asthmatic seizures of eighteen months' duration. The patient had generalized sarcoidosis involving the lungs, mediastinal and peripheral lymph nodes, spleen, thyroid gland and pleura. Bronchoscopy revealed marked narrowing of the right stem bronchus with some mucosal thickening. Tissue removed from the bronchial wall showed tuberculoid granuloma without caseation. There were many giant cells. The patient's condition improved and a bronchoscopy performed several months later showed normal-looking bronchi. The biopsy was not repeated.

Vogt (7) found lesions of sarcoidosis in the walls of the bronchi of a 58 year old woman at necropsy. The bronchial mucosa appeared dusky but no obstructive lesions were present. Other organs affected were the lungs, lymph nodes and spleen.

It is apparent that the submucosa of major bronchi can be the site of sarcoidosis lesions. The incidence of this localization cannot be estimated, since few patients having the disease have been submitted to bronchoscopy. Even fewer have had bronchoscopic biopsy performed. This is understandable in view of the relatively indistinctive gross appearance of the lesions. In the two cases reported here, there was mucosal thickening. Among the five cases reported by others, only one showed easily visible nodules (3). Removal of tissue by biopsy is necessary if the lesions are to be recognized. The findings in Case 1 suggest that normal-looking mucosa can contain the granuloma. It remains to be shown whether random bronchoscopic biopsy, like liver and bone marrow aspirations and muscle biopsy, can be a useful, diagnostic measure in patients suspected of having sarcoidosis.

All instances of bronchial wall involvement thus far reported have been in patients with enlargement of the mediastinal lymph nodes. In Case 1, there had been considerable regression in the size of the nodes during the year preceding bronchoscopy.

In most cases, there was evidence of external compression of major bronchi by the enlarged nodes. Yet, in none of them was the appearance of the mucosa significantly altered in the compressed areas. It seems, therefore, unlikely that the granulomatous lesions found in the submucosa represented extensions from adjacent lymph nodes. The lymph node capsule acts as an effective barrier to such extension. Sarcoidosis, unlike tuberculous lymphadenopathy, does not cause softening of the affected nodes. Mucous membrane lesions of the upper

respiratory tract arise independently of contiguous lymph node involvement, and it may be assumed that bronchial lesions also are intrinsic in origin.

Recent reports indicate that the walls of bronchioles can be the site of involvement when pulmonary nodulation is present. Spain (8) found diffuse granulomatous infiltration of the bronchiolar walls in a lobectomy specimen of a patient with sarcoidosis. Coates and Comroe (9) studied pulmonary function in sarcoidosis and found that bronchiolar narrowing was an important source of functional abnormality.

SUMMARY

Two cases of sarcoidosis with involvement of major bronchi are reported. In both instances, the microscopic finding of non-caseating epithelioid-cell granulomata on bronchoscopic biopsy was unexpected. In the first case, broncholithiasis with pulmonary suppuration was the presumptive diagnosis; and in the second, bronchiogenic carcinoma. Infrequent bronchoscopic biopsies in sarcoidosis may explain the rarity of reports on bronchial localization.

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THE JEWS' HOSPITAL AND PSYCHOLOGICAL MEDICINE

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The centenary mark in a hospital's life, no less than in a man's life, is a significant event. That mark has been reached this year by The Mount Sinai Hospital of New York—the Jews' Hospital as it was named for the first fourteen years of its life. While the broad record of its first hundred years has just been written (1), this is the second in a series of communications*** prepared on special aspects of the Hospital's life. These are being written in the light of Cicero's definition of history, as "the witness of the times".

The Jews' Hospital's role in the field of psychological medicine was distinguished only by the fact that it was one of a handful of voluntary general hospitals in America at the time to admit mentally ill patients and to treat them as patients. This, of itself, is significant when it is recalled that when the Jews' Hospital was founded Dorothea L. Dix had, only a short time before, embarked on her crusade that was to shape the humane care of the mentally ill for the next hundred years.

As a general hospital, the Jews' Hospital's management of the mentally ill patient was far in advance of the practices of its contemporaneous public asylums and private sanatoria which were characterized by restraints, physical violence and "shock treatment". At the same time, the Jews' Hospital had not advanced much beyond what was generally known by the well-trained general practitioner of the day. And these practices continued to reflect many of the stereotypes handed down by Benjamin Rush fifty years before.

Witness then the times; but first, Rush. His view of mental illness itself is a good instruction. He divided it into two main groups—general and partial intellectual derangement. His treatment likewise was divided into two main groups—those methods applied to the mind through the medium of the body and those applied to the body through the medium of the mind.

Among the specific methods of treatment he espoused and which were popularly adopted throughout the country were the use of depleting agents, *i.e.*, bloodletting, purgatives and emetics. Venesection was a method he employed regularly and sometimes to the point of ex-sanguination. In one patient, he is reported to have extracted 200 ounces of blood within a few months and from another, 470 ounces in 47 bleedings.

Many of Rush's contemporaries, both in America and Europe, shared his enthusiasm for bloodletting. Esquirol, who succeeded Pinel at the Salpetriere in Paris, wrote in 1816: "On the discovery of the circulation of the blood, it was

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*** See bibliographical reference No. 2.

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believed that we had discovered the cause of every disorder and a remedy for all illness. Blood was shed abundantly. The blood of the insane was the more freely shed as by bleeding them to faintness, it was believed that they were cured. This treatment was extended to all the insane." . . . This was done on the principle that "the blood being too abundant or too much heated ought to be evacuated or cooled" (3).

Venesection as Rush and his contemporaries practiced it and other forms of bloodletting by leeches and cupping were based on the theory that mental disease represented "a great morbid excitement or inflammation of the brains; that an unrestrained appetite caused blood vessels to be overcharged with blood; and that it is most important to relieve the brain before obstruction and disorganization takes place" (4). This, of course, was a considerable advance over the previously held views that mental illness represented a form of bedevilment, an invasion of the body by evil spirits, or a morbidity of the humors.

Treatment, nonetheless, followed these more primitive views in that it involved chiefly the extraction or withdrawal from the body substances held to contain the source of the disease. This was the rationale which underlay venesection and other forms of bloodletting as well as the use of purgatives and emetics. The use of hot and cold douches as a form of treatment in mental disease was likewise related to the then prevalent view of mental illness being seated in the blood stream. Thus, stimulation or retardation of the circulation by douches was believed to be helpful.

This was some of the Rush inheritance that had carried over from the eighteenth into the mid-nineteenth century. By the 1850's, however, members of the recently-founded Association of Medical Superintendents of American Institutions for the Insane—the precursor of the American Psychiatric Association—were beginning to challenge these concepts. The challenge was neither vigorous nor loud enough to influence medical practice. Truth is, moreover, that even these specialists did not break sharply with the Rush tradition.

Treatment of the mentally ill in the 1850's by those specialists most active in the organization of the A.M.S.A.I.I. consisted of hydrotherapy, vesication, purgation and depletion. The literature of the time is replete with references to prolonged baths—hot, tepid and cold—warm or cold douches and warm baths accompanied by cold applications to the head. Samuel B. Woodward (5), one of the fathers of the A.P.A. precursor, favored warm baths with cold applications to the head principally in the treatment of mania.

F. T. Stribling, another founder of the A.P.A. precursor, in commenting on vesication, stated that with few exceptions when general practitioners referred patients to a mental hospital they sent them in "well bled, blistered and purged" (6). Woodward (7) himself claimed that vesication was useful in the treatment of some cases of melancholia particularly when the blisters are applied over the epigastrium in the presence of indigestion. He also stated that blistering is indicated in different forms and stages of dementia. Woodward held, however, that *setons* and *issues* gave no benefit in ordinary cases of melancholia.

Pliny Earle, another one of the founding fathers of the A.P.A. precursor, reported on the therapeutic use of ulceration of the scalp through the application of *setons* and *moxas*. Moxas were chiefly applied to the vertebral column in cases of melancholia. The use of laxatives and cathartics in the treatment of mental illness uniformly was common practice in the mid-nineteenth century. Although Woodward (9) disapproved the administration of strong cathartics, he admitted the usefulness of laxatives since "it is common for the bowels to be constipated in mania". He also recommended the use of stomachics and laxatives in cases of melancholia and of dementia.

By the mid-nineteenth century, despite the currency of venesection by the more conservative practitioners, there were signs of controversy beginning to emerge among the specialists in psychological medicine on the value of depletion. But even these specialists were not prepared to deny the possible value of topical bleeding. Woodward, for example, admitted the usefulness of local bleeding in cases of mania with attendant cerebral congestion. He denies, however, the value of this technique in dealing with ordinary cases of melancholia. Pliny Earle's extensive review of this subject indicates that American specialists generally agreed that venesection was not beneficial and indeed might be harmful. The prevailing opinion of these same specialists, however, was that cupping and leeching is admissible and in fact desirable in some cases, particularly to relieve congestion of the brain and when applied to the thigh and the vulva, in cases of amenorrhea.

This then, in brief outline, was the climate of the times when the Jews' Hospital was founded and, as can be seen from the histories taken from the first Case Book of the Hospital, reflected the practices in psychological medicine.

ILLUSTRATIVE CASE HISTORIES

Suppressio Mensium

Admitted April 11th 1906. At 20 domestic native of Germany, born in this country 2 years. Suffer from suppressio mensium of 6 months standing. has much leucorrhoea, and is generally debilitated. - no signs of pregnancy manifest. Though the abdomen is much swollen, Ordered warm bath, and 8 pills morning and evening of the following composition:

℞. Fule Albi

" Rhei

" Salapae

Extract Sarsaparilla ℥ss

℥l Sumpson

M. Capiae aa qtt xv. M. et divide in pill aa qviii

April 10th Has been complaining of pain in the head all the week, and today has some stringency from Tinct. Cartharidis which she has been taking in 5 drop doses in diet. Ordered to stop Cartharidis, and take

Potapae Nitrici ℥j

" bitartaric ℥ij

Aqua Lunatica ℥ss

" Limas ℥ss

M. et take 2 pills every 2 hours.

April 21st. Stringency has been relaxed but the general symptoms are unimproved, and bowels are again constipated. Ordered

Sennae Albi ℥ss

Rad Rhei ℥ij

(Supremo aqua ferri ℥ss)

mixt Potapae Nitrici ℥ss. M. et take 2 pills every 2 hours

April 23. Ordered atropine injection for prostr. albus. April 24th Ordered

Hydruy Gelatini qviii

Aqua purae ℥ss. M. et use

as injection.

The treatment was continued till April 25th, without the least benefit. Ordered 97 Ferrum ℥ss.

Take 10 drops in diet.

May 2nd. Discharge is better but has had no return of menses - and the abdomen becoming more and more swollen. face is flushed and has nervous manifestation from the nose: bowels entire. Ordered Fule Albi Comp 40 grs, and continue use of warm pedicure every night as usual.

May 3rd. Symptoms unchanged. still complains of cephalalgia and a burn of descending, with quick pulse and hot skin. Ordered.

Potapae Nitrici ℥j

" bitartaric ℥ij

Aqua purae ℥ss

" Limas ℥ss. M. et take 2 pills every 2 hours.

May 4th. Not so much food, and pain somewhat relieved. Ordered Fule Albi Comp 40 grs.

May 6th. Ordered Potapae Nitrici ℥ss

" Rhei 40 grs. take at once

Comment: The case history concludes with the following observations:

During the whole of her treatment there was no change worthy of note . . . save for an increase and decrease of pain with slight attacks of hysteria. . . . Discharged. . . . Somewhat stronger, but not the least improved in her catamenial function.

Congestio Cerebri from an attempt at hanging

Age 21, single, native of Oberndorf, Wurtemberg. Suffering from Congestion of the Brain, brought on by an attempt at suicide, induced by disappointment in love. She has been for some time engaged to her cousin—and he very strangely wants to postpone marriage. After being disappointed twice she undertook to destroy her life

by hanging herself from a gas house, in the house of her employer in 1881; but fortunately the house was insured. before she accomplished more than a good choking. Her mind is much disarranged and she manifests a marked stultification. Pulse is full and strong, eyes very much congested; ophthalmalgia great, bowels very costive—Ordered 6 cups to back of neck and a table spoonful of the following every morning.

1/2 drachm Niter Sy
" 1/2 drachm Sy

1/2 drachm Sy - M. S. Followed by 20 drops of every hour

of Magnesia Sulphat gr
" 1/2 drachm Sy

May 11th. Symptoms unchanged; pulse 105 & full. eyes much blood-shot, tongue coated and dry and bowels costive. She seems impressed with the idea that God will now forgive her for her attempt at suicide & at times gives vent to her feelings in tears, and is obstinate in refusing her a medicine. Bowels seem much congested—Took 12 oz of blood by cups to the back of the neck & gave Magnesia Sulphat gr. 4 continued cold applications to the forehead & nuchal internally.

May 12th. Has slept very little since admitted to the hospital, and continues for bedding. Same treatment continued; pulse 100 & tongue dry. Has had a catamenial flow, but this combined with the loss by cupping seems to leave her pulse very little. now does it relieve the head ache, congestion of the eyes or flushed face.

May 13th. Pulse 90 & tongue dry marked. Continued treatment.

• 10th. Pulse much better but is very costive. Ordered

1/2 drachm Niter Sy

" 1/2 drachm Sy

" 1/2 drachm Sy

" 1/2 drachm Sy

Followed by Magnesia Sulphat - One medicine only operated used.

May 14th. A much better & during the evening seemed in good spirits and was laughing. pulse 80, skin cool, and ophthalmalgia very little.

May 14th. Has been constantly improving & is now, when she seems perfectly rational eats and drinks regularly.

May 16th. Has considerable headache from constipation. Ordered

1/2 drachm Niter Sy

" 1/2 drachm Sy

and to day and not to morrow - This medicine operated & the bowels were opened & she was discharged May 18th, cured

M. J. Lunnard M.D. All Physicians

Cured

Melancholia

Native of Stamburg, aged 20 people. Admitted July 17, 1886.
 Melancholia. Suffering from melancholy in consequence of disappointment in love. About two months since while on her way from Stamburg to New York she unfortunately made the acquaintance of a young man, who offered her a short term of matrimony, furnished her marriage, under the impression that she possessed a fair amount of wealth; but shortly after, in learning that the main object of such marriage could not be attained, he unconsciously told her that all intercourse between them must henceforth be discontinued. She immediately became insane, and wholly disconsolate desired to throw herself into the sea, and in various other ways attempted to destroy her life. In a few days her desire to destroy herself became less arduous, and she sank into a disconsolate dreamy state, in which she has remained up to the time of her admission. Ordered cold douches to the head, night and morning.
 July 18th came as yesterday. slept well after 12 until morning. General health good.

July 20th P's apparently rational but is disinclined to hold any conversation. Ordered
 In Valerian 3ss Zj
 - Asafetida . Zj
 In Cinchona C Zjss In Liny 2 hours 1/2 transpirable.

Aug. 1st Condition both mental and physical the same as when admitted. Occupies her time by needle work, and reads a book occasionally, but seems apparently unconscious of her actions at times when no one is near. Replies rationally when questioned but never speaks unless first addressed.

Aug. 13th Since last note her condition has been nearly the same. The douches same as she bathes have been continued and occasionally given to act upon the admitted. Bowels and efforts of a moral tendency have been made to console her or bring about reaction of the mind, but in vain. Removed by her friends.

G. M. Plummer, M.D. Physician

Dysmenorrhoea Mania Hysterica

Aged 20, single, native of Posen. . . Her father states that fourteen days since during her menstrual period she began to evince symptoms of aberration of mind by speaking incoherently and expressing unnatural desires. He procured medical aid but the treatment proved unavailing as the symptoms have continued to grow more alarming up to the present time. Presents a wretched, emaciated appearance—is sleepless—refuses food, has frequent tonic spasms—pupils largely dilated and expression vague. Pulse 60 and tongue coated white. After repeated efforts she was forced to swallow sedatives but without effect. A quarter of a grain of Morph. sulph. was then given every half hour until one grain had been taken, but she still remained sleepless and very boisterous. Aether sulph was then administered by olfaction which was successful in producing a temporary quietude.

. . . Has been restless during the day but has taken a moderate amount of food. At 8 P.M. not having urinated in 24 hours and being apparently in pain from distension of the bladder it was emptied by catheter, and Morph. sulph. again ordered.

. . . Was more quiet during the night but is in the same condition as yesterday. Ordered a blister over the sacrum. . .

. . . Is more docile apparently from exhaustion—bowels have moved and has taken food. P.M. From 1½ a grain of Morph. sulph. sound sleep was produced.

. . . Has awoke perfectly rational. Complains bitterly of the blister. To have Morphium again at night.

. . . Appetite voracious—countenance cheerful and converses sensibly. Ungt. Sabinæ et Cantharides to be continued.

... Continues rational—general condition good. Ungt. sabinae to be discontinued.

... Up to present date has improved in general health, mind remaining undisturbed. Left Hospital cured.

... Readmitted in the same condition as when previously admitted—being now perfectly maniacal. Her period of menstruation has passed without the appearance of the discharge.

... Nymphomania had rendered mental alienation complete: Her obscenity became disgusting, and it was necessary to tie her hands and feet to prevent her doing violence to herself and those around her: She would throw herself out of the bed so that that had to be made on the floor, tear all garments from her person, pull her own hair, and tear books, linen or whatever else came to hand.—The cold douche was applied to her head with temporary good effects, but neither Hyoscinamus and Camphor—Valerian—Laudanum in drachm doses nor Morphia ad libitum could control her and produce sleep and quiet. She was this day discharged not improved, and transferred by her father to Wards Island and from there to the Lunatic Asylum.

Monomania

Born in Altenhausen, Bavaria, age 23 years, Single, Domestic. . . . Until a few days ago she was perfectly well except that her bowels usually were more or less costive. Last week she had her courses, and three days ago she was first heard to express, as a fact revealed to her during the night preceding by providential inspiration, that she was going to get married before the close of the day together with some languages she is said never to have used before, expressive of what her friends call unnatural desires, etc. In vain did the latter appeal to her reason and modesty. She could not be called to behave immodestly before strangers but still persisted in her monomaniacal idea. On admission her appearance betokened amateness, face flushed, mouth voluptuous, eyes moist and fiery. She could with difficulty be induced to stay, expecting to get married every moment as she had for 3 days past. Who the bridegroom was she did not yet know but she averred that the Almighty

had disowned her & she avowed somebody had used subtly, as I determined
as his wife. She was evidently in a state of excitement. Her pulses was very
enacted, tongue coated, bowels very costive. After a bath with cold omels, or
Jerdon cut cold cloths to head which fairly burred, & exhibited

R. O. Phelps. Hammon. 90x

East Abington Co. 9.11

A. Fishii

affli. *Pellaea* xat. *Prorhynchus* *Hernand.* one bird

It was hard work to make her swallow the pill & towards night she became particularly symptomatic. Morphine, with great difficulty administered, was needed to produce the slightest rest.

May 27. Patient converses perfectly rationally on all subjects but her intended marriage. At this her ideas are unaltered. She is untroubled by other phobias, she is very amiable. Pulse given for 15 minutes. She speaks. Color of head face diminished. Leg. Prof. Smith administered the enema given at night.

May 28. Complaints of some difficulty in passing water w/ painful sensations in genitalia as if something heavy was hanging down from the part. Doual revealed nothing abnormal except a relaxed, flabby condition of the part, especially of the labia minora, clitoris rather large & abnormally sensitive. Face still flushed, pulse full & bounding, tongue dark red, tongue &c. &c.

P. Potass Nitrat (3)

Arch. et Bot. Part. gr. *Adiantum*, xij. l. 3. *Pinus* *Engl.* *apud*

June 3. Patient as regards her monomaniacal ideas is unchanged though physical symptoms & condition ameliorated. She is discharged.

Not improved is to be hoped for.

S. M. Plummer, Esq.,
Providence, R. I.

S. L. Osberg,
Yonkers, N. Y.

Ecphronia

Native of Hoehspeyer Bavaria, age 23 years, Single, Domestic. . . . Her personal appearance is rather fine-looking, robust and plethoric. She is exceedingly uncommunicative, and because she won't talk at all, seems very stupid. Her pupils are perhaps more than naturally dilated. She looks melancholy and pensive. Pulse not too frequent, but strong and full. Menstruation generally regular; has menstruated 2 weeks ago. Tongue coated whitish Bowels costive, and extremely sluggish unless medicine is taken. Nothing satisfactory can as yet be made out of her history since she will not at all talk. She acts sullenly and obstinately; and yet has apparently no energy or will of her own. Must be told to do all she does specially. She complains of nothing but if pressed very much to answer, will talk of an intensely aching pain in abdomen (which on touch shows nothing abnormal) and of a burning heat on top of head.

. . . At night her extremities especially feet were found very cold. Rubbed with mustard and heated bricks applied to feet. Early part of night restless and uneasy, wants to go out of Hospital but after midnight fell into quiet, natural sleep.

. . . Her melancholy, flushed face, strong full pulse and untalkativeness unchanged. Feels some relief from having bowels moved freely. . . . 8 cups applied to back of neck drawing probably from 7-8 ounces of blood from her. This gave momentary relief to headache but soon after felt just as before.

. . . No change whatever. On admission after a general bath with douche had been given a gentle douche was ordered for 10 minutes daily and in the meantime cold cloths to the head. The douche has been accordingly daily applied but seeming to increase the headache and heat and pain, it was today ordered to be discontinued. Cold cloths applied continually. Hot mustard foot bath every evening. The pills which she has thus far been taking regularly produce copious daily stools.

. . . Not much improvement in her uncommunicative disposition. She likes best to be alone, and can sit hours, almost entirely without moving. Nothing is left untried to interest her in something—but all to no avail. Answers questions slowly and only after repeated asking. Is almost never seen to laugh or of her own accord to talk. Avers to ascribe her condition to a severe fall she had in January last whereby she hurt her head, and soon after which she says, commenced her indifference to every thing around her. She is conscious of her condition, but takes no interest in it. She says she dont talk because she cant think of anything to say. All her thoughts being mixed up and undefined. She talks to nurse patients and every body else much less than to me (Dr. E.). She does not seem to be very amative at present, though from the first sexual love was suspected in some way connected with or causing her melancholy. In *no* manner, has it so far been possible to discover with certainty that she was ever disappointed or crossed in love. General bloodletting talked off.

. . . Patient sleeps very well, has good appetite and looks hearty. Pulse very full. Tongue clean.

. . . Counterirritation is established on back of neck by issue produced by solid Agent Nitras and kept up by issue peas: two days later dressed with Unguent. Sabina.

. . . Again ordered one of the Croton Oil Pills to be taken morning and evening's—feels greatly worse if her bowels are not well cleared out every day. No change except that heat and pain in head are less severe and less frequently, a little. No change in general condition.

. . . Patient has now been in hospital over five weeks. She said that she had menstruated two weeks before that time. Ordered to bring on the discharge mild diet, warm food and hip-baths, and Tinct. Valerian. Ammoniat. 25 drops every 2 or 3 hours. Query: Might she not have commenced uterogestation?

. . . The Tinct. Valerian seems to excite her bowels to too vigorous action and diarrhoeal, painful discharges, and is replaced by copious droughts of an infusion of Rad. Valerian and Cont. Cinnamomi. No improvement; no appearance of menstrual discharge.

. . . Since this day last week no change whatever is apparent. Warm mustardfootbaths have been from the beginning and are still given.

She now . . . has 2 leeches applied to each temple every other day.

. . . The treatment indicated . . . is still followed except that the powders she takes since yesterday contain instead of Calomel, Aloes and Gum Acacia, each: . . . She has now been in hospital 2 months. No signs yet of menstruation. General health excellent, but she is still nearly as melancholy and untalkative as when admitted. It is now ascertained from her that she was in love, and was prevented from marrying her lover, had a child by him, which in some unaccountable way died shortly before her melancholy commenced.—She also confesses the possibility of her being again in the early months of pregnancy.

. . . Discharged, somewhat improved. That is she speaks somewhat easier when addressed.

COMMENT

The foregoing cases records have been transcribed almost in their entirety as examples of the clinical practices in psychological medicine in the United States in the mid-nineteenth century. Accordingly, no attempt has been made in this report to evaluate or critically assess these practices as reflected in the case histories.

More important than the cases and practices themselves is the fact that The Jews' Hospital at a time when psychiatric cases were handled almost exclusively by "insane asylums", jails and homes—was one of the first voluntary general hospitals in this country to admit and treat them.

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THE OSTEOHISTOLOGY OF THE NORMAL HUMAN VERTEBRA*

ITS RELATION TO SCOLIOSIS AND CERTAIN LESIONS INCIDENT TO GROWTH AND SENESCENCE

EDGAR M. BICK, M.D.

INTRODUCTION

The growth, maturity and senescence of the human vertebra has not heretofore been recorded from the point of view of its osteohistology. Excellent studies of its embryology (11), its morphology, and its comparative anatomy (12, 20, 21, 24) have appeared during the past 25 years. Histological specimens related to specific problems have been illustrated and described frequently. Of fundamental interest were those published by Schmorl and Junghans (16, 23) who first clarified the general histology of the human vertebra. The longitudinal growth in the vertebrae of certain laboratory animals has been studied by Bisgard and Musselman (9), and by Haas (13). A detailed study of diaphyseal growth of the vertebral body in man, the development of its apophyseal ring, and its regressing osteohistology during senescence were recently described from this laboratory (6, 7, 8). The mature vertebra has been illustrated often, and its microscopic architecture is that usually displayed in text-books of anatomy and histology. However, these are usually single plates and give to the reader no impression of the normal histological variations found in any group of such specimens. As will be seen later, these normal variations are important points of reference in determining early pathological changes in vertebral bone.

A proper understanding of the progressive osteogeny of the human vertebra has become increasingly desirable in recent years for a number of very cogent reasons other than the appealing fact of its not having as yet received adequate attention. The introduction of a novel and possibly important approach to the therapy of scoliosis, following the work of Bisgard (9), Haas (13), and Arkin (2) in experimental scoliosis, and of Nachlas (19), Kleinberg (18) and others in experimental surgical epiphyseodesis of the spine, established a principal need for a more accurate recording of vertebral growth. The basic premise of the work of these investigators was and remains the existence of functioning growth plates in the body of the human vertebra comparable to those found in certain laboratory animals such as dogs and rabbits.

The invention of a relatively simple and safe method for obtaining trephine biopsy samples from the human vertebra by Valls (30), and by Siffert and Arkin (26), may make the use of this procedure far more widespread than it is at present. It also makes more necessary the establishment of a base of reference of normal histology of the vertebra in the various age groups, a reference not as yet to be found in available publications. Re-evaluation of such lesions as Scheuermann's adolescent kyphosis by Schmid (22), senile osteoporosis by Aschoff

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(3), Albright (1) and Steindler (27), osteoarthrosis and osteophytosis by Collins (10), Scott (25), Johnson and Alexander (15) and others (4), and the comprehensive studies of the normal and pathological physiology of the intervertebral disc by Keyes and Compere in the United States (17), Collins in England (10), and by Sylvén (29) and Hirsch (14) in Stockholm, have required an equal re-evaluation of the process of development and regression of the normal vertebral body.

The method of study chosen for this purpose was the only one feasible for human specimens, comparable to those available for laboratory animals. The distinction was merely one of the time taken to collect specimens. In order to establish a life-long standard of reference for the osteogeny of the human vertebra, it was necessary to accumulate a complete series of proper samples. Therefore, specimens were removed from fresh autopsy material consisting of cases known to have been free of musculo-skeletal lesions involving the spine or skeleton generally. A preliminary series of such specimens was exhibited at the meeting of the American Academy of Orthopaedic Surgeons in February, 1950. The illustrations herein presented as the *Atlas* are the completion of this project.

Specimens range from that of an 8 cm. foetus, approximate age 14 foetal weeks, to that of a 90 year old female. Foetal specimens were measured from crown to rump and their ages calculated on the basis of tables published by Streeter (28). In those age groups where male and female specimens were apt to vary, that is, mid-adolescence and late middle age, samples of both sexes are given. In other age groups samples are interchangeable, and therefore do not require repeated duplication.

It must be noted at this point that the *Atlas* begins at an age in which the general form of the human vertebra has been developed. It does not include that earlier embryonic stage in which the provertebra is developing from the scleroderm. Briefly, the scleroderm which surrounds the embryonic notocord forms a mesenchymal mass of which one part, the anlage of the vertebral mass, is known as the centrum. This mass divides into two parts, a cephalic and a caudal. This formation has an important phylogenetic and embryologic interest, but is not properly concerned with the project in hand. The human type vertebra is formed by a juncture of the adjacent halves of two centra, that is, the caudal part of one and the cephalic part of its neighbor. In the first specimen of the *Atlas* this juncture has already occurred, and the only possible, if not probable, remnant of the previous structure is the point of exit of the major veins at the central part of the posterior wall. For readers with a special interest in this provertebral stage, Gadow's monograph is definitive (12).

DESCRIPTIVE SPECIMENS

FOETAL

Figure 1. 8 cm. foetus. Approximate age 14 weeks (foetal). The body of the vertebra is composed chiefly of early connective tissue. Cartilage cells have begun to form in the center of the area.

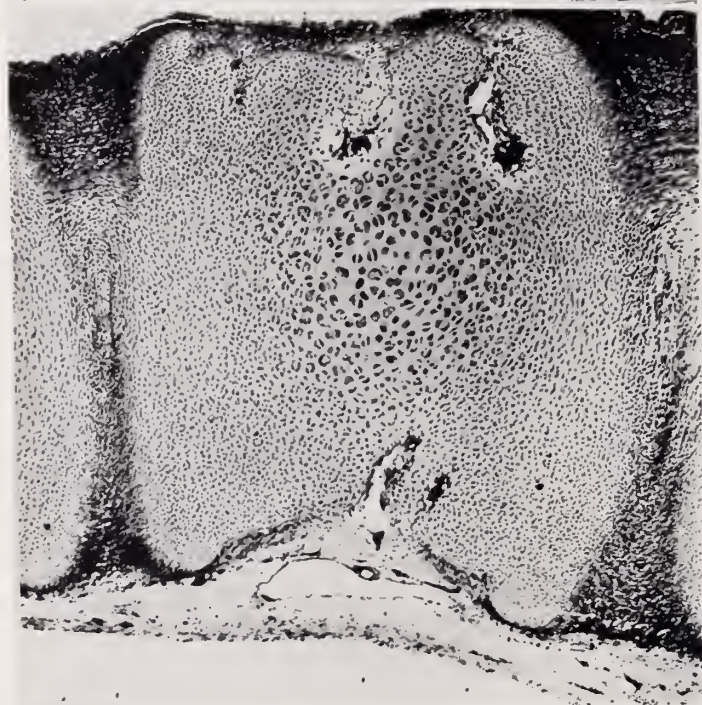


FIG. 1

FIG. 1. 8 cm. fetus, 14 week (foetal). The body of the vertebra composed chiefly of young connective tissue. Cartilage cells have begun to form in the center of the area. This is the beginning of the rigid vertebral column.

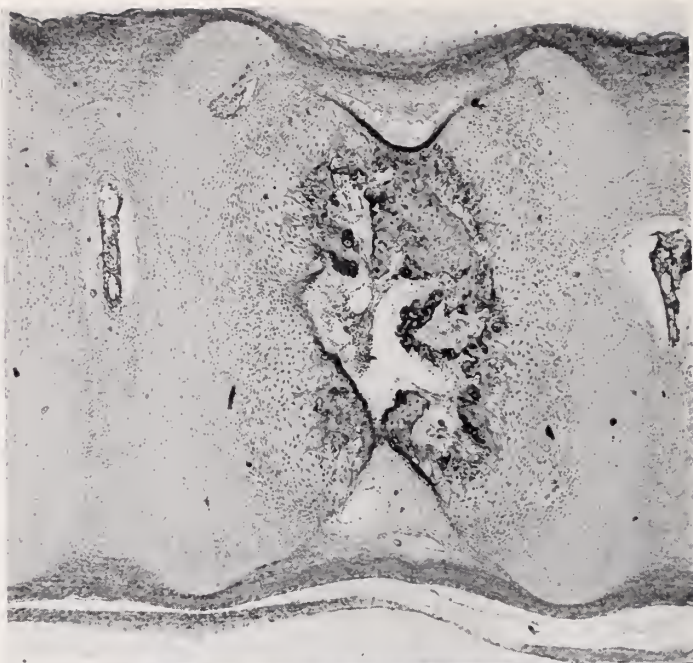


FIG. 2

FIG. 2. 10.2 cm. fetus, 15 week (foetal). The first evidence of osteogenic tissue forming within the enlarging cartilaginous center.

This is the beginning of the rigid vertebral column. The form of the vertebra has already been fixed by mesenchymal derivatives. This incidentally furnishes further evidence for the hypothesis maintained by most morphologists that the anatomic structure of bone is pre-formed by the embryo, and only the superficial details of its form are influenced by the normal pressures and tensions of anti-gravity forces during active life. Further evidence in support of this view will be indicated in subsequent sections.

The intervertebral discs consisting of the nucleus pulposus and annulus fibrosus are already in their proper positions relative to the vertebra. The anterior and

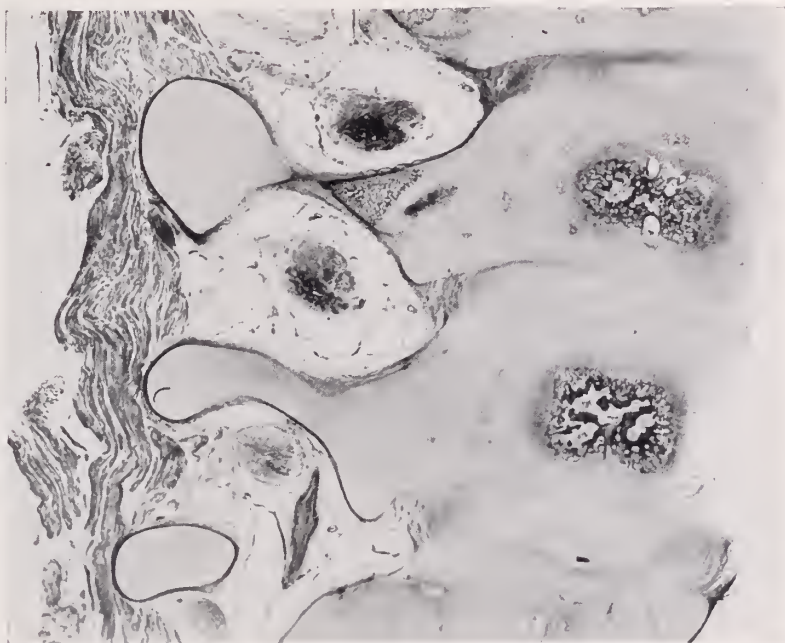


FIG. 3. 14 cm. foetus, 18 week (foetal). The osteogenic center has begun to square off in lines characteristic of the vertebral body.

posterior longitudinal ligaments, which will play a most important role in the maintenance of vertebral posture in all later periods, are already visible and well developed.

Figure 2. 10.2 cm. foetus. Approximate age 15 weeks (foetal). The cartilaginous field is now enlarged and calcified, and the first evidence of osteogenic tissue is seen forming within its center about advancing blood vessels. The significance of the relationship between these two phenomena, that is, osteogenesis and the invasion of blood vessels, recalls a collateral problem in osteogeny itself dating back to Haller in the 18th century and still unresolved, but beyond the scope of this work. Nevertheless, the association of newly formed blood vessels and osteogenesis *de novo* at this point should be well noted. The cartilage mass,

meanwhile, has expanded, but still occupies only about one half of the vertebral body.

Figure 3. 14 cm. foetus. Approximate age 18 weeks (foetal). The osteogenic center is now well formed and has begun to square off in the lines characteristic of the vertebral body. The ossific area has also begun to exhibit some trabecular architecture but it still presents the irregularity and greater vascularity of pri-



FIG. 4. 21 cm. foetus. 25 week (foetal). The ossific center has reached the periphery of the vertebral body. No appositional bone has appeared from periosteum or perichondrium. Columnar cartilage makes its first appearance across the cephalic and caudal surfaces of the ossific mass. These are the diaphyseal plates. (Note in the text that the term diaphyseal plate is used synonymously with and in place of the former and as yet more common term epiphyseal plate.)

mary bone. Later these will acquire the more compact and regular structure of definitive bone.

Figure 4. 21 cm. foetus. Approximate age 25 weeks (foetal). The ossific center has now reached the transverse periphery of the vertebral body. It should be noted that as yet no appositional bone appears from the periosteum or perichondrium of the vertebra to supplement enchondral growth.

At this time columnar cartilage makes its first appearance across the cephalic and caudal surfaces of the ossific mass, forming true diaphyseal plates. (Cf. Figures 5 and 8.) This formation, the columnar arrangement of cartilage cells, is the

characteristic of bone expanding into pre-existing cartilage during growth. It must be remembered that, in the growth of mammals in general, the phylogenetically primary cartilage of the skeleton does not turn into bone by metaplasia, but is replaced by bone growing from established ossific centers, as seen in the preceding sections of this *Atlas*. In such enchondral ossification, at least

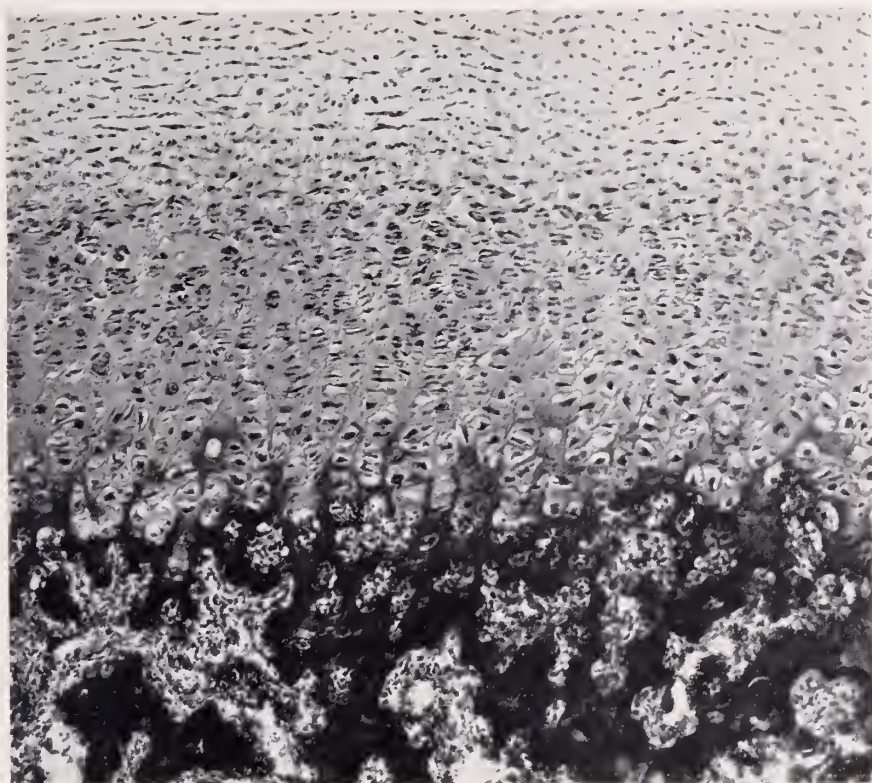


FIG. 5. High power view of Figure 4 showing the diaphyseal plate in detail. Along the lower third are the ossific trabeculae. Along the upper third is flattened cartilage characteristic of the type found in all articular cartilage. Between these two layers large cartilage cells are grouped in a linear form suggesting a palisade of columns. This layer in all diaphyseal bone marks the advancing ossific diaphysis.

in bones which enlarge in an axial direction, the histologic element which marks the advance of bone trabeculae is this plate of cartilage cells which has assumed the columnar form.

Because this formation was first noted in long bones of the limb skeleton, and there lies between the shaft, or diaphysis, and the appended epiphysis, it was thought to be related to growth of the latter and was named epiphyseal plate. However, the term diaphyseal plate is not only the preferable one but, on functional grounds, the correct one, since the formation is osteogenetically related to growth of the ossific mass of the diaphysis.

The diaphyseal plates may replace either epiphyseal cartilage or articular

cartilage, depending upon which lies ahead of the diaphysis in its longitudinal axis. In the long bone of the limb, they replace epiphyseal cartilage. In the vertebra they replace articular cartilage. The difference is functional and not histological. The epiphysis itself, when present in the bones of the limb skeleton, grows longitudinally by means of the activity of its own articular cartilage, replaced by bone trabeculae from its own center of ossification. *Neither at this stage nor later does an epiphysis form beyond the diaphyseal plate in the human vertebra.*

Figure 5. Magnification $\times 100$. This is a high power view of the diaphyseal plate from the cephalic border of the ossific mass exhibited in *Figure 4*. Above the dark stained bone trabeculae is the area of surface (articular) cartilage. At their connecting surfaces the cartilage begins to assume the columnar structure characteristic of diaphyseal growth in the long bones of the extremities. The irregular shapes of the transitional cartilage between the columns and the flattened cartilage cells approaching the articular surfaces are equally characteristic. Among the bone trabeculae immediately below the columns can be seen clumps of degenerating cartilage cells, the result or perhaps the stimulus of advancing ossification.

The broad subject of enchondral ossification cannot be included in this discussion, but the reader with special interest will find it fully discussed in the standard current literature on osteogeny (5).

CHILDHOOD AND ADOLESCENCE

Figure 6. 3 day old male. This is the earliest post-natal specimen in the collection. The ossific mass is well formed. The light-shaded intervertebral connective tissue (annulus fibrosus) sets off the now completely calcified cartilage of the unossified juxta-articular portion of the vertebral body.

Trabecular structure has assumed a predominantly vertical orientation (anti-gravity), apparently in anticipation of, rather than as a result of, the impending assumption of orthograde posture. This must of necessity be the result of stresses and strains effected by biologically inherent muscle tensions. Such situations in the animal economy come perilously close to appearing teleological.

Figure 7. 4 day old female. At this age there is no discernible difference between male and female specimens. The ossific development is therefore similar to that described in *Figure 6*. The close approximation of the posterior longitudinal ligament to the ossific mass is quite visible in this section. Its point of closest contact marks the area thru which the largest of the intra-osseous vessels enter into the vertebral body.

Figure 8. Magnification $\times 100$. This is a high power view of the cephalic diaphyseal plate of *Figure 7*. The characteristic columnar formation is more distinct than in the earlier specimens exhibited under high power (*Figure 5*), and the trabecular structure is more mature.

Figure 9. 4 week old male. Further development of the ossific mass, and more evident stress orientation of trabeculae is seen in this section of a one month old infant.

Figure 10. 6 week old male, and Figure 11. 8 week old female. These sections



FIG. 6. 3 day old male. This is the earliest post-natal specimen in the collection. The structure of the bone trabeculae has assumed a predominantly vertical, or anti-gravity orientation, apparently in anticipation of, rather than as a result of the impending assumption of orthograde posture.

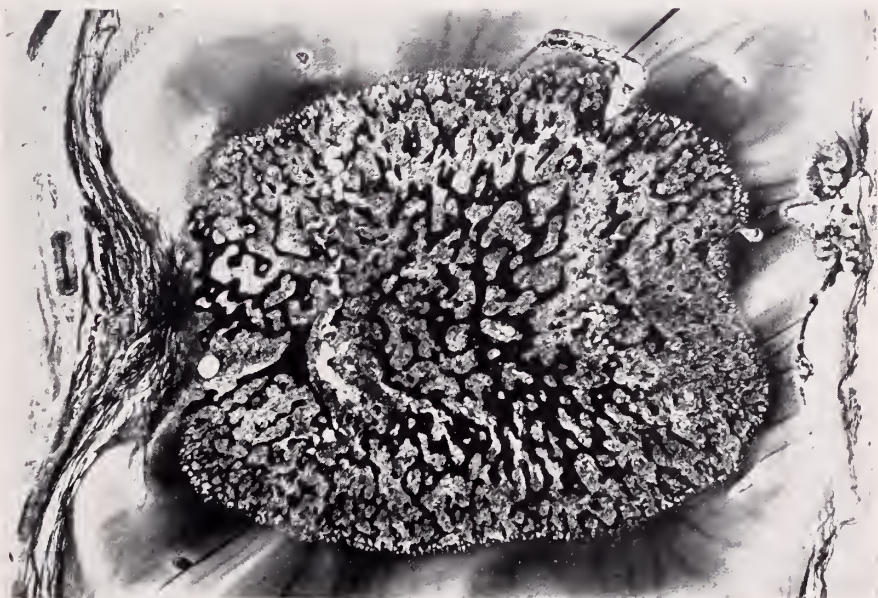


FIG. 7. 4 day old female. At this age there is no discernible difference between male and female specimens. In this section the close approximation of the posterior longitudinal ligament to the ossific mass at the point of entry of the intra-osseous vessels is well demonstrated.

show increasing development of trabecular structure, and demonstrate again the similarity of male and female vertebrae in infancy.

Figure 12. 3 month old male. In this specimen the ossific mass has assumed the shape it will maintain thru babyhood and early childhood.

The depressions at the edge of the cephalic and caudal surfaces of the ossific mass, appearing as rounded corners in this sagittal section, do not begin to fill

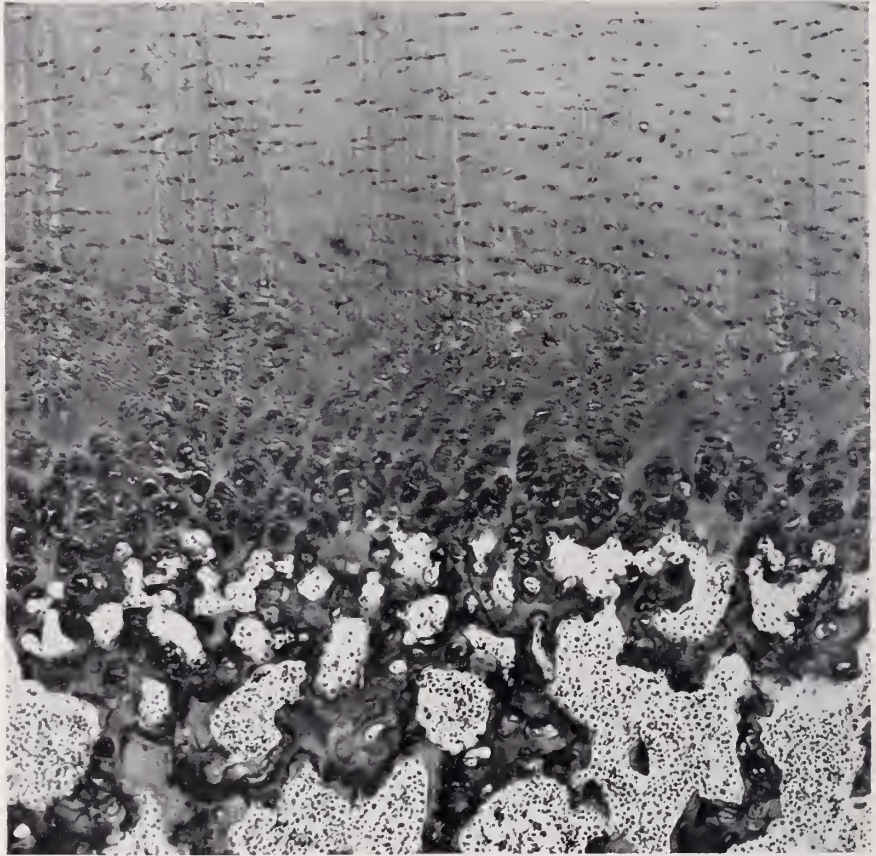


FIG. 8. This is a high power view of the cephalic diaphyseal plate of Figure 7. The characteristic columnar cartilage form is more distinct than in the earlier specimen (Figure 5), and the advancing trabecular bone is more mature.

in with bone until after the 6th to 8th year. At that time the ring apophysis will form in these areas (v.i.). It must be noted that the depressions which appear as corners in a sagittal section represent a depressed circular rim about the ossific mass. When the vertebral body is viewed intact from the superior or inferior surfaces, however, this ossific depressed rim is not at all visible since it is covered by the almost level surface of the articular cartilage. If it could be detached, the articular cartilage structure would appear as an inverted cap or saucer.

Figure 13. 6 month old male. In this specimen the insertion of fibers from the

anterior longitudinal ligament into the anterior rim of the articular cap can be clearly seen. It must again be emphasized, for reasons which will appear later, that this is the site of the future ring apophysis. (Cf. comment, *Figure 12*.)

These fibers represent a portion of a ligament which exerts a strong anti-gravity pull against dorsi-flexion of the trunk; that is, they tend to prevent the human from falling backwards. It is the principal check ligament of the anterior vertebral musculo-fascial mechanism. Its traction force at the site of insertion of its separate fibers is therefore considerable.

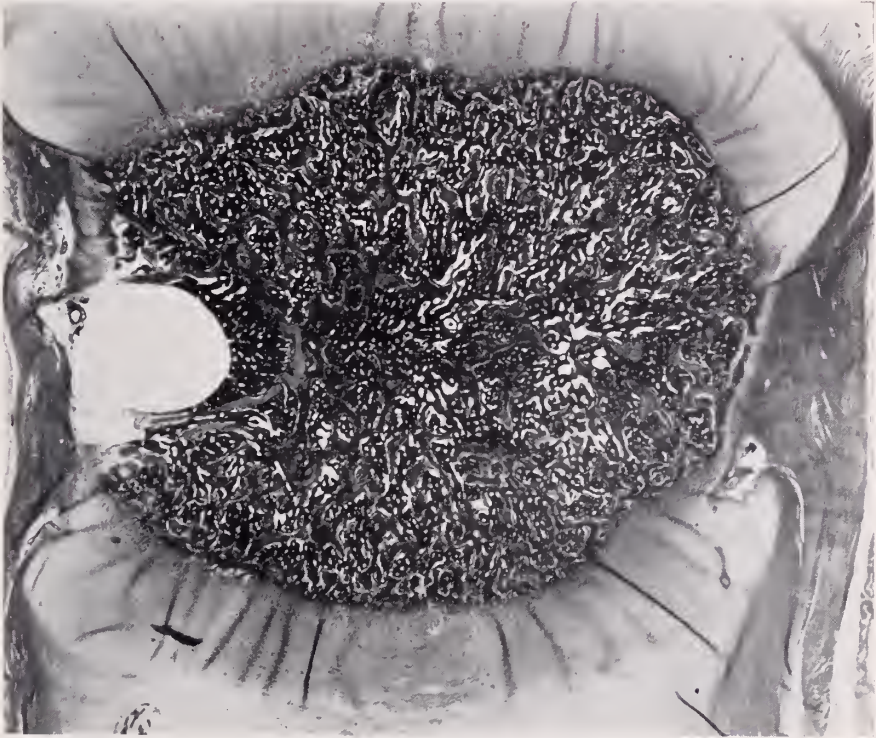


FIG. 9. 4 week old male. The stress orientation described at birth in Figure 6 is more evident in this one month old infant.

Figure 14. 8 month old male. By this time, after the early weeks of daily periods of sitting propped up, the forces of gravity have been added to the intrinsic stresses on the trabeculae and the vertebral ligaments.

Figure 15. 1 year old male. This section exhibits the rounded corner of the broad cartilaginous articular cap particularly well. The importance of this area has been discussed in previous paragraphs.

Figure 16. 2 year old male. The nucleus pulposus surrounded by annulus fibrosus is well marked in this specimen. The expanding pressure of the nucleus against adjacent articular surfaces forms a mutually resistant mechanism influencing

FIG. 10

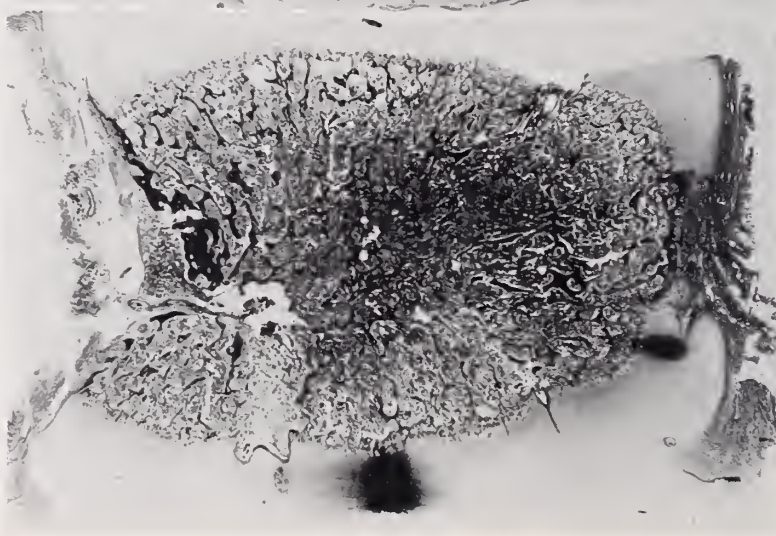
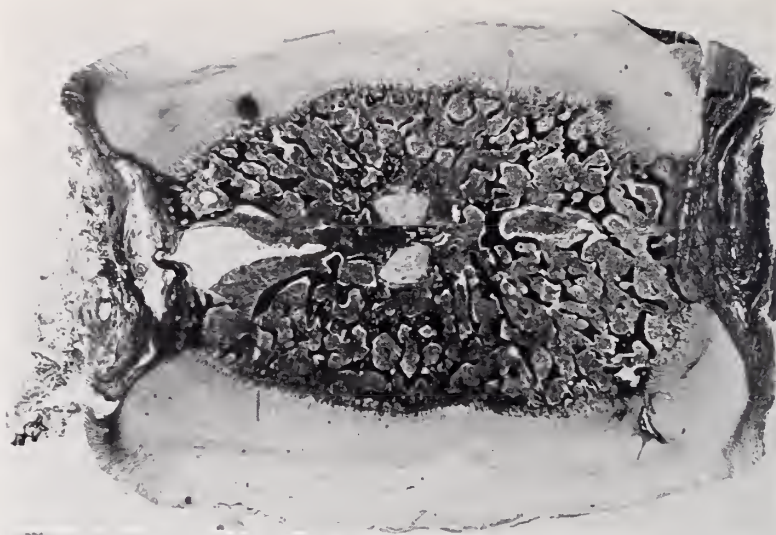


FIG. 11

FIG. 10. 6 week old male. The bone formation is forming a more definite specific pattern, and occupies a larger area within the vertebral mass.

FIG. 11. 8 week old female. There is still no discernible structural difference between the male and female specimen.

the form of both. However, under normal circumstances the positive pressure is from the nucleus. This is significant in relation to adult and senescent specimens, and of course in connection with certain pathological states (v.i.).

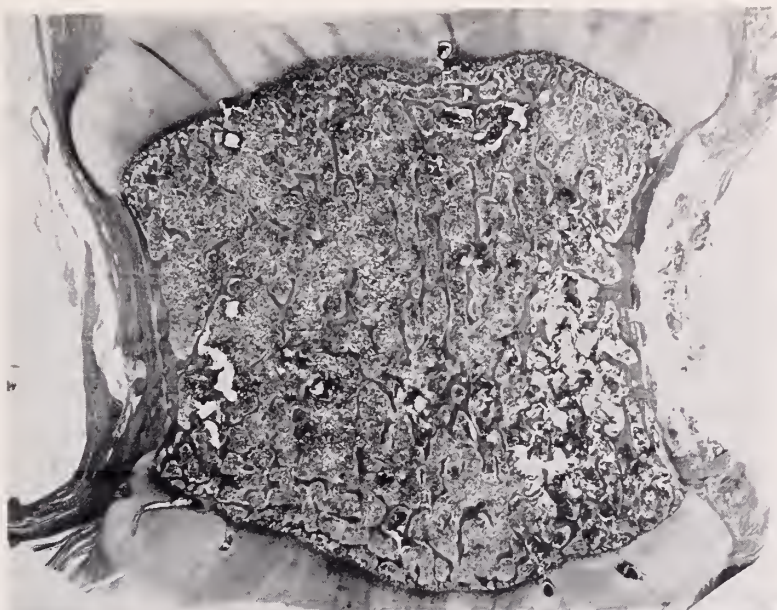


FIG. 12



FIG. 13

FIG. 12. 3 month old male. In this specimen the ossific mass of the vertebral body has assumed the shape it will maintain thru babyhood and early childhood. The cartilaginous dips which appear at the corners of the ossific mass, appearing as rounded edges in this sagittal view represent the flat surface section of what is actually a circular rim surrounding the cephalic and caudal borders of the bone substance of the vertebra.

FIG. 13. 6 month old male. Note here the clear demonstration of the insertion of fiber from the anterior longitudinal ligament into the anterior rim of the articular cap. These fibers are from a ligament which exerts a strong anti-gravity pull; it is the principal check ligament of the anterior vertebral muscular mechanism. Its traction force at the site of insertion into each vertebra at this point is considerable.

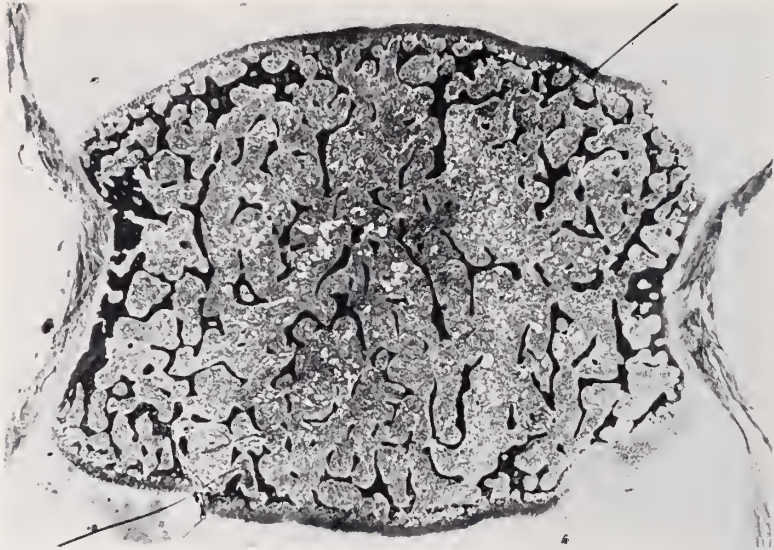


FIG. 14. 8 month old male. At this time there have been some weeks of daily sitting up. The forces of gravity have been added to the intrinsic stresses on the trabeculae and the vertebral ligaments. The trabeculae are therefore even more obviously predominantly vertical.

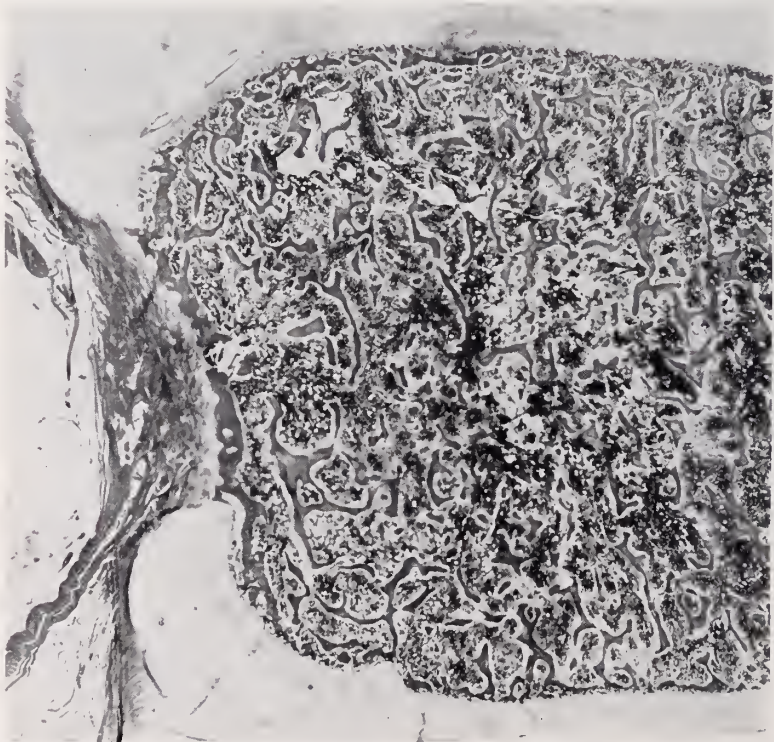


FIG. 15. 1 year old male. The anterior rim of the cartilaginous cap is particularly well seen in this specimen. Its importance will be apparent in later sections.

Figure 17. 3½ year old female. Note the progressive increase in the density of trabeculation. The child is now walking and running freely.

Figure 18. 5 year old male. The ossific mass now occupies all of the vertebral body except for the cartilage caps covering the articular surfaces. This specimen exhibits a good view of the relatively large nucleus pulposus of childhood surrounded by the connective tissue fibers of the annulus fibrosus.

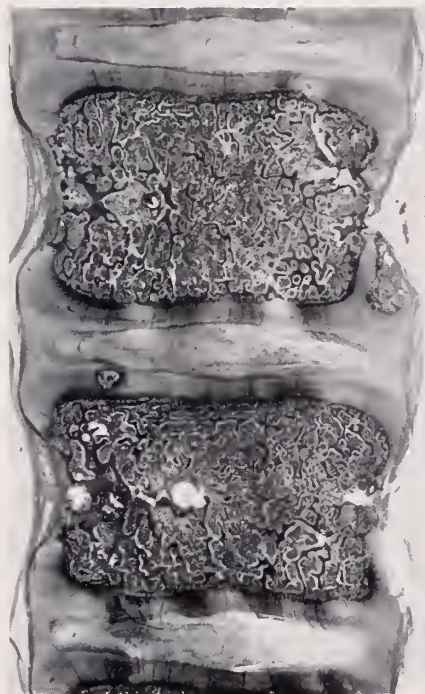


FIG. 16

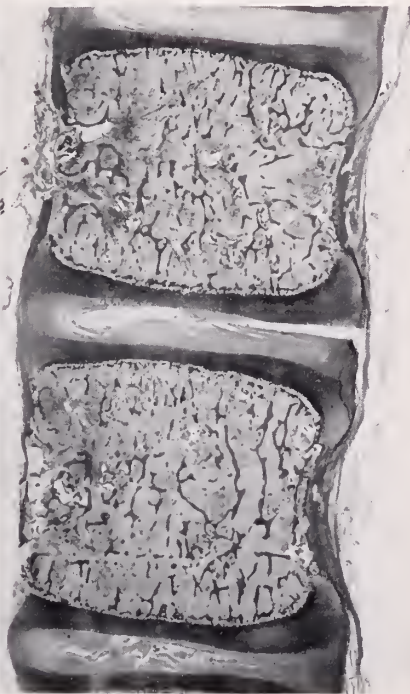


FIG. 17

FIG. 16. 2 year old male. The nucleus pulposus surrounded by annulus fibrosus is well demonstrated in this specimen. The expanding pressure of the nucleus against adjacent articular surfaces form a mutually resistant mechanism influencing the form of both.

FIG. 17. 3½ year old female. Note the progressive increase of density of trabeculae and cartilage. The child has now been walking and running freely.

The pressure of the nucleus may cause a depression along the center of the ossific mass. This is almost always temporary in a normal vertebra, and it should not be confused with a similar appearance in older specimens which accompanies, to a greater or lesser degree, senile or pathologic osteoporosis.

Figure 19. 6 year old female. Adjacent corners of a sagittal section. This is the first specimen to exhibit an area of calcification in the depression of the cartilage cap. a) Ossific mass of the vertebral body. b) Intervertebral disc and annulus fibrosus. c) Condensation of calcified cartilage in the peripheral rim of the articular cap. d) Insertion of fibers of the anterior longitudinal ligament. e) Diaphyseal plate.

This is a particularly important specimen. The small area of calcification in

the anterior depression of the cartilaginous cap (c in the illustration) marks the earliest stage in the formation of the *vertebral ring apophysis*. The peculiar importance of this structure in the human vertebra will be discussed more suitably under General Comment, after its development has been illustrated in succeeding sections.

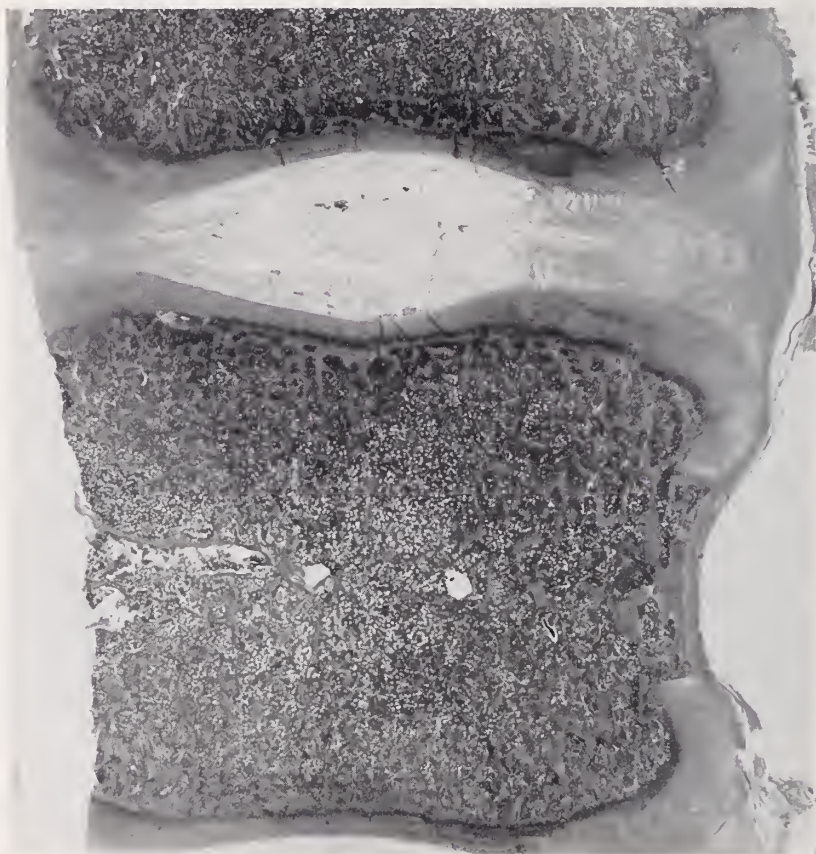


FIG. 18. 5 year old male. The ossific mass now occupies all of the vertebral body except for the cartilage caps covering the articular surfaces. This specimen exhibits a good view of the relatively large nucleus pulposus of childhood surrounded by the connective tissue fibers of the annulus fibrosus.

Figure 20. 8 year old female. In this specimen the early condensation of the vertebral ring has not as yet appeared. The age of its appearance varies from 6 years as in *Figure 19* to 8 years as in *Figure 21*.

Figure 21. 8 year old male. The signs of very early condensation of the vertebral ring are visible in several of the anterior corners of the cartilage cap.

Figure 22. 10 year old male. This section exhibits further condensation and calcification of the area of the vertebral ring. *This appears entirely outside the ossific mass and therefore outside the diaphyseal growth plate.*

Figure 23. 13 year old female. The first clear evidence of ossification in the vertebral ring is seen in this section (e). It is important here to note that it lies clearly outside the diaphyseal plate (e), and only at the extreme periphery is it in line with the longitudinal axis of growth of the vertebral body. Fibers of the longitudinal ligament can be seen leaving the main bundle and inserting into the

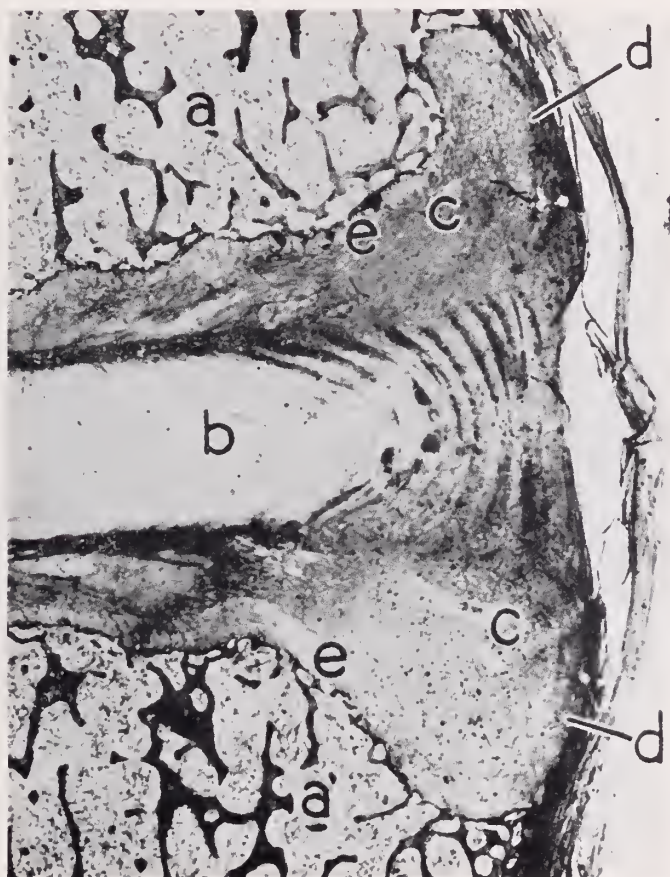


FIG. 19. 6 year old female. This is the first specimen to exhibit the formation of the vertebral ring apophysis, as yet only as calcified cartilage. a) bone trabeculae of ossific mass. b) nucleus pulposus (intervertebral disc). c) calcified cartilage forming vertebral ring. d) insertion of fibers of anterior longitudinal ligament. e) diaphyseal plate.

area of the vertebral ring (d). It is this relationship which classifies the vertebral ring apophysis as a *traction apophysis*, since it lies in position to withstand the strong and constant pull of this powerful ligament in the human orthograde position. (Cf. comment, *Figure 13*.)

Figure 24. 13 year old male. At this age the female vertebra is apt to be more mature than the male. In this male section the ring apophysis does not yet show evidence of ossification.

Figure 25. 14 year old female. Illustrating further development of the ring apophysis in the female.

Figure 26. 14 year old male. The ring apophysis still shows no evidence of ossification in this male specimen.

Figure 27. 15 year old male, Figure 28. 16 year old male, and Figure 29. 17 year old male. Somewhere between the 15th and 17th years ossification of the ring apophysis occurs in the male. It has occurred within a range two years earlier in the female. (See *Figures 23 and 25.*) In *Figure 29* ossification of the ring is already well advanced and beginning to fuse with the vertebral body mass. As will be seen in the following specimen (*Figure 30*), this stage of incipient fusion of the ring is about the same in male and female. Altho starting later, fusion

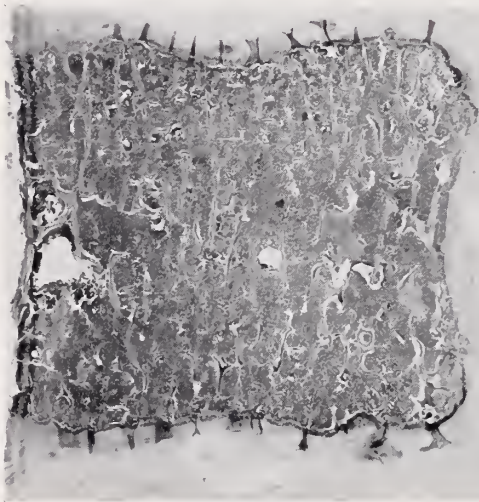


FIG. 20

FIG. 20. 8 year old female. In this specimen the condensation of the vertebral ring has not yet appeared. The age of its first appearance varies from 6 years to 8 years. (See following Figure.)



FIG. 21

FIG. 21. 8 year old male. Early signs of condensation of the vertebral ring are visible in the anterior corners of the cartilage cap.

apparently progresses more rapidly in the male and both attain skeletal maturity, at least in the vertebra, at about the same time.

Figure 30. 17 year old female. The ossified vertebral ring apophysis is beginning to fuse with the body ossific mass to a degree not perceptibly different from that in the male specimen of *Figure 29*.

Figure 31. Magnification $\times 100$. High power view taken from *Figure 30* showing the gradual disappearance of the columnar cartilage formation in favor of flat articular cartilage. Along with this is a levelling off of the surface trabeculae of subchondral bone.

It should be noted here that the so-called subchondral bone plate is never a continuous osseous surface. It is composed of flattened trabeculae interspersed with areas of marrow, that is, it is a surface of spongy bone and not a cortical layer.

These marrow openings are the channels thru which cartilage, under pressure of the expanding nucleus pulposus, may be driven into the end-plates of the diaphysis to form the nodular incursions known as Schmorl's nodes (23). (See Figure 35.)

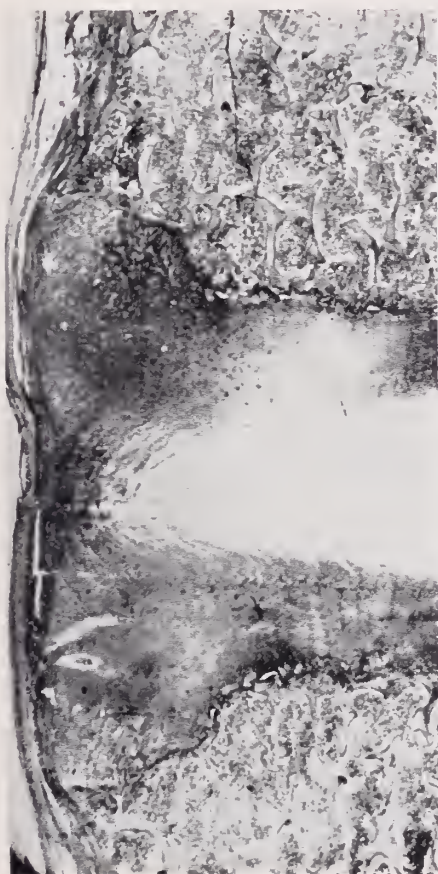


FIG. 22

FIG. 22. 10 year old male. Further condensation and calcification of the area of the vertebral ring. Note that this appears entirely outside the ossific mass and therefore outside the diaphyseal growth plate.

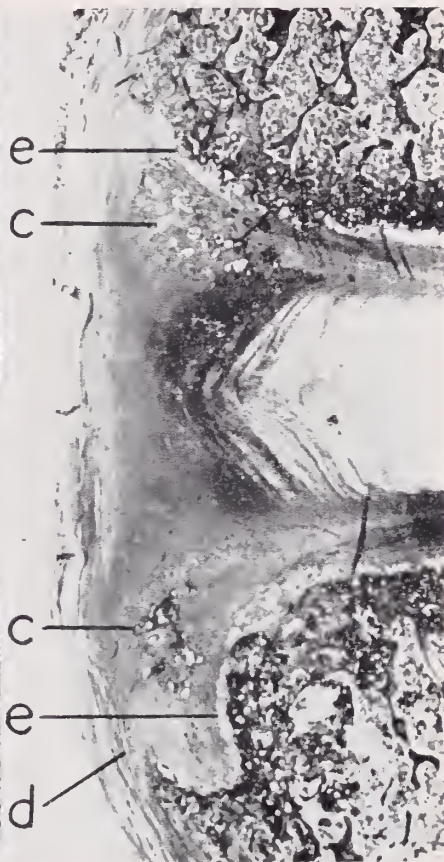


FIG. 23

FIG. 23. 13 year old female. The first clear evidence of ossification of the vertebral ring is seen in this section. (c). Note again that the ring lies outside the diaphyseal growth plate (e), and is not in line with the longitudinal axis of growth of the vertebral body. Fibers of the anterior longitudinal ligament are seen inserting into the area of the ring at (d). It is because of this arrangement of accessory ossification center and ligament insertion that the ring meets the definition of a traction apophysis.

ADULT

Figure 32. 18 year old female. The ring apophysis is now completely fused with the ossific mass of the body.

The ring has attained its own growth outside the area of ossific development

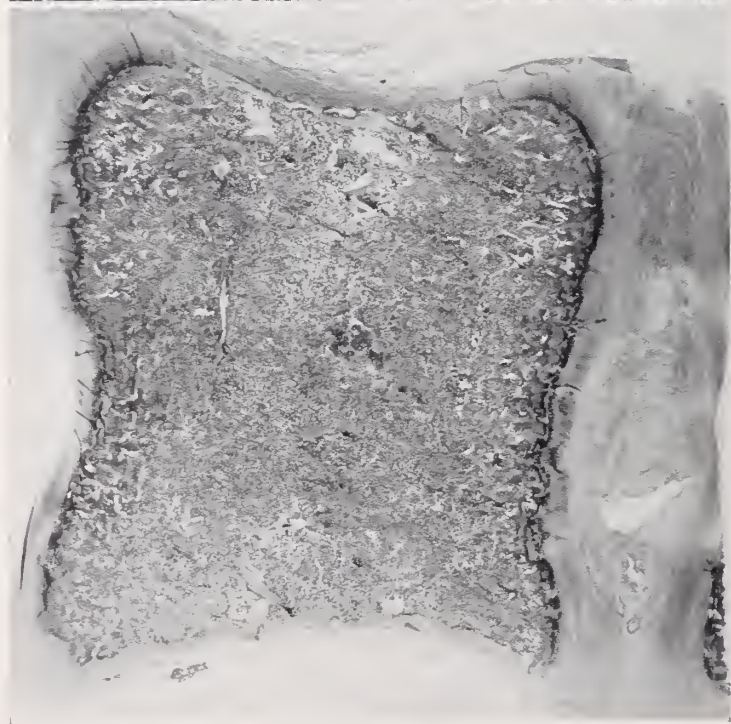


FIG. 24

FIG. 24. 13 year old male. At this age the female vertebra is more mature than the male. Therefore in this section the ring apophysis is not as yet ossified.



FIG. 25

FIG. 25. 14 year old female. Further development of the ossified ring apophysis. Bone trabeculae extending toward the vertebral mass.



FIG. 26

FIG. 26. 14 year old male. The ring apophysis still shows no sign of ossification in this male specimen.

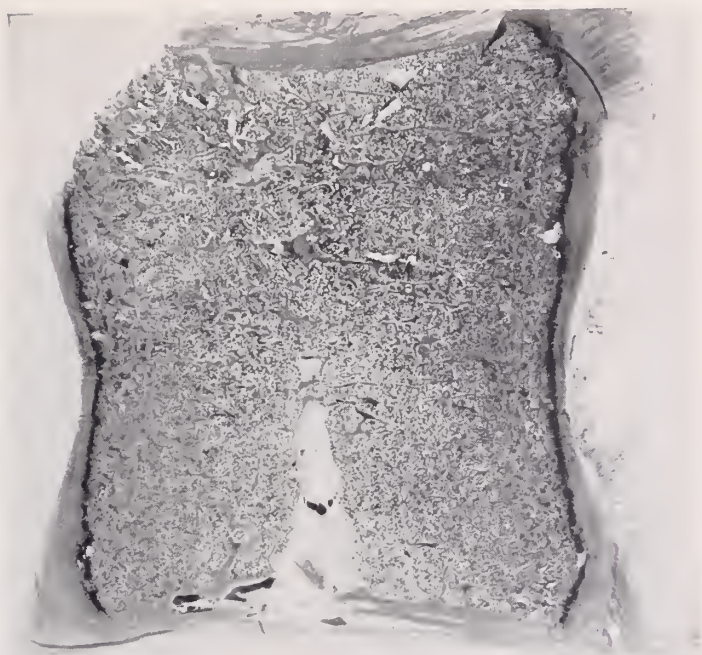


FIG. 27

FIG. 27. 15 year old male. Altho in the female the ring is by now well developed, it is still not beyond the stage of calcified cartilage in the male.

of the body mass, around its cephalic and caudal periphery. It has added nothing to the growth of the vertebra. Its own elevation above the vertebral mass has merely displaced what would have been part of the cartilage cap except, perhaps, for a slight peripheral eminence of a millimeter or so. This would form the peripheral rim of the vertebral body seen from the superior or inferior line of vision. In no way, therefore, does the vertebral ring conform to the definition of an epiphyseal structure. It complies fully with that of a traction apophysis. (This matter was discussed in more detail in the comment on *Figure 4*.)

Figure 33. Magnification $\times 100$. High power view of the diaphyseal boundary. Columnar cartilage has entirely disappeared. The subchondral plate of bone is now capped by dense, flat, articular cartilage. Intertrabecular marrow spaces



FIG. 28

FIG. 28. 16 year old male. There is still no sign of the ring apophysis ossification in this male specimen.

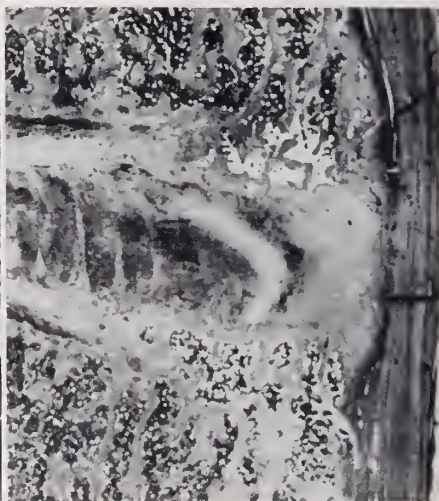


FIG. 29

FIG. 29. 17 year old male. Somewhere between the 15th and 17th year ossification of the vertebral ring apophysis occurs in the male. This is in a range of two years later than in the female.

are visible as in *Figure 31*. This formation makes the mature, adult, vertebral body, and will persist until senescence sets in.

Figure 34. 18 year old male. The diaphyseal plate has almost completely disappeared. The structure of the vertebral body is the equivalent, structurally, of that of the female of the same age.

Figure 35. 23 year old female. Adult vertebra. Note the well rounded corners of the ossific mass, the predominantly vertical trabeculae, and the slight concavity of the four sides of this sagittal section. The darkly stained area at its upper border is an incursion of fibrocartilage and nuclear material. This is the histological appearance of a Schmorl's node. (Cf. comment, *Figure 31*.)

Such formations were found to be common occurrences in Schmorl's vast autopsy experience. From the clinical point of view they are not generally con-

sidered pathologic. It is therefore, with this reservation, included in the *Atlas*. The intrusion of this material into the vertebral mass takes place first thru the intertrabecular marrow spaces of the subchondral plate and then expands thru the spaces of the spongiosa, rarely beyond 0.5 cm. in diameter, and usually less extensively.



FIG. 30. 17 year old female. The ossified vertebral ring is beginning to fuse with the ossific mass of the body. At this age the male and female ring apophysis are not perceptibly different. The male development, while delayed in starting to ossify, has caught up with the female.

These formations are sometimes referred to as herniations of the intervertebral disc, which of course they are in respect to the bone of the vertebral body. They must not be confused, however, with herniations of the disc into the foramen vertebralis (spinal cord canal). The similarity of names is an accident of terminology which should be corrected.

Figure 36. 34 year old male,

Figure 37. 43 year old male,

Figure 38. 48 year old female,

Figure 39. 48 year old male,

Figure 40. 50 year old male,

Figure 41. 52 year old female,

Figure 42. 58 year old female.

The Figures 36 thru 42 are sections of adult male and female specimens. These figures, exhibited together with *Figures 32 thru 35*, represent an adequate sampling of eleven normal adult specimens selected from our collection to com-

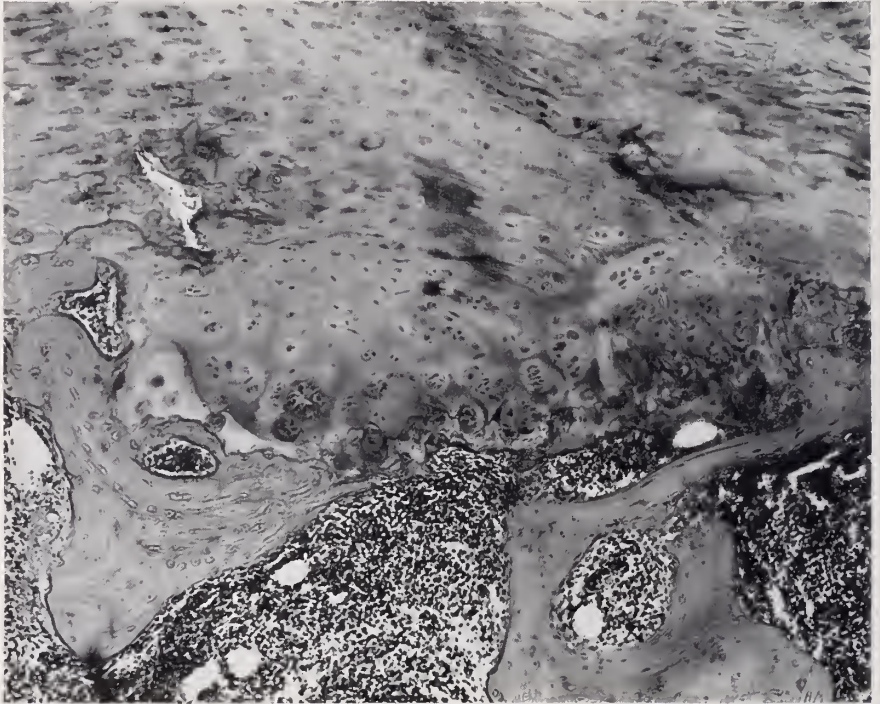


FIG. 31. High power view taken from Figure 30 showing the gradual disappearance of the columnar cartilage of the diaphyseal growth plate. It is being replaced by the flattened cells of the articular type of cartilage tissue.

plete a chronologic series. They serve as points of reference against pathological specimens obtained by biopsy or at the operating table, especially those obtained during the early questionable stages of a lesion or dyscrasia.

Certain generalities in their appearance are notable. First of all, it is apparent that there is no discernible structural difference in the osteohistological appearance of the normal male and female vertebra between the end of adolescence and the beginning of senescence. This structural similarity in the internal architecture is in terms of density of trabeculation, thickness of trabeculae, cellularity of the spongiosa, and depth and density of the articular cartilage. This similarity between the sexes in normal specimens does not contradict the fact that certain

abnormalities, such as osteoporosis, may appear more frequently in females than in males.

Note the normal variations in the concavity of the cephalic and caudal surfaces of the vertebral ossific masses. It is these masses which establish the appearance of vertebral form when viewed in x-ray films. The recognition of such

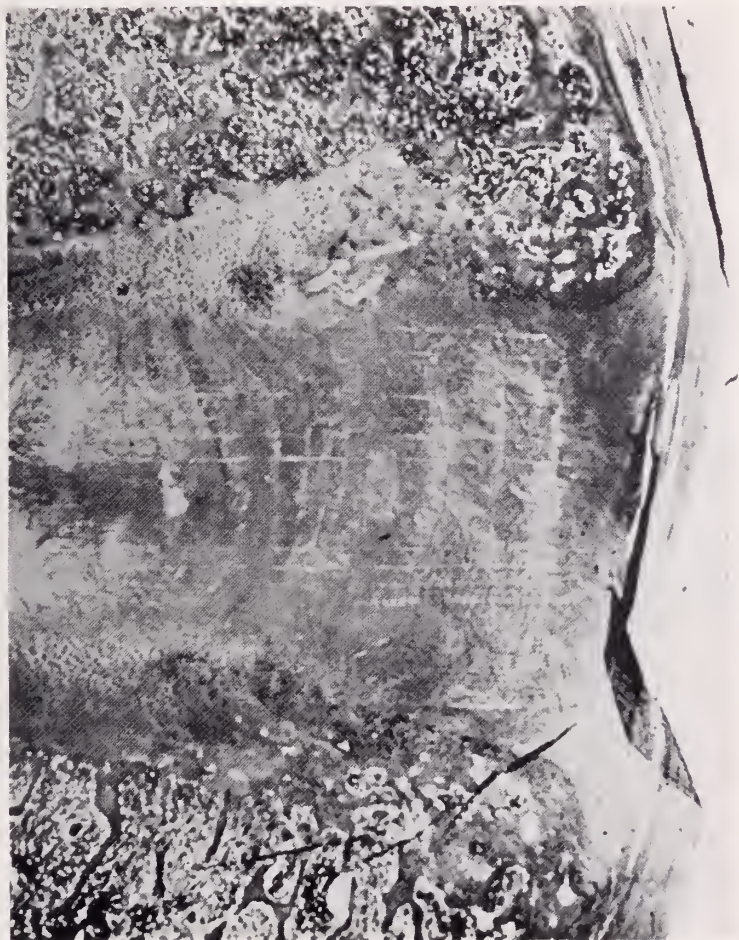


FIG. 32. 18 year old female. The ring apophysis is now completely fused with the ossific mass of the vertebral body.

variations in contour becomes clinically important in judging the significance of similar concavities in x-ray films which suggest senile osteoporosis or hyperparathyroidism (fish-tail vertebrae). The degree of exaggeration of these concavities determines the clinical interpretation between normal and pathological; between normal resistance to the pressure of the nucleus pulposus, and collapse of vertebral trabeculae due to deproteinization.

In a similar fashion other criteria of pathological states which appear ordinarily as abnormal exaggerations of normal trabecular or cartilaginous forms must be gauged against a collection of normal variations such as those presented here. Among the abnormalities occurring in adult decades which come easily to mind, besides osteoporotic lesions, are Paget's disease of the vertebra in its early form, the common haemangioma, and certain generalized osteosclerotic diseases. These do not ordinarily present clear-cut pathognomonic cellular appearances, and are interpreted rather on the trabecular architecture of the available specimen.

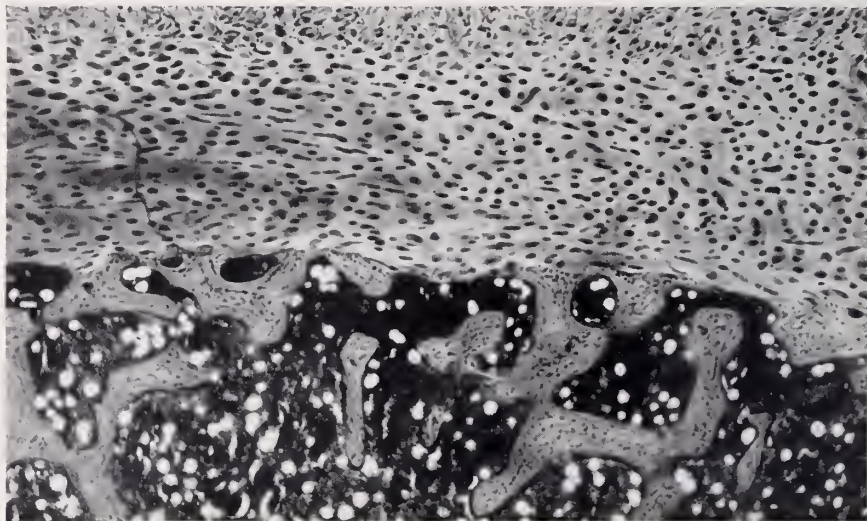


FIG. 33. High power view taken from the diaphyseal body of Figure 32. Columnar cartilage has now entirely disappeared. The subchondral plate of bone is beautifully illustrated in this section. It is composed of the dark stained trabeculae of the lower half of the plate, with the flattened bone surfaces lying adjacent to the articular cartilage. Note well that the subchondral bone plate is not a solid osseous band. The spaces between the trabecular ledges have an important bearing on certain lesions frequently found in asymptomatic spines.

SENESCENCE

Figure 43. 62 year old male. This section is the first in this series to show the thin and relatively sparse trabecular structure of senescence.

This osteoporosis is not the result of decalcification. It is due to deproteinization, or rather failure to replace protein in bone trabeculae during the normal cycle of replacement and resorption which constitutes the continuing process of ossification in the living organism. Senescence has been defined as that period in life when the normal balance between tissue replacement and tissue resorption is broken in favor of the latter. In bone this process is particularly evident in the failure to replace bone protein in the matrix of the trabeculae, while protein loss continues at a normal or perhaps accelerated rate. In the absence of a normal supply of this specifically osseous protein, new bone salts will not precipitate and old deposits will be absorbed by humeral or phagocytic activity.



FIG. 34

FIG. 34. 15 year old male. The diaphyseal plate has disappeared in this male specimen as in the preceding female. FIG. 35. 23 year old female. This specimen is that of a fully developed adult vertebra. Note the well rounded corners of the ossific mass, and the slight concavity of each of the four sides of this sagittal section. The darkly stained area at the upper border is an incursion of cartilage and nuclear material, a so-called Schmorl node.

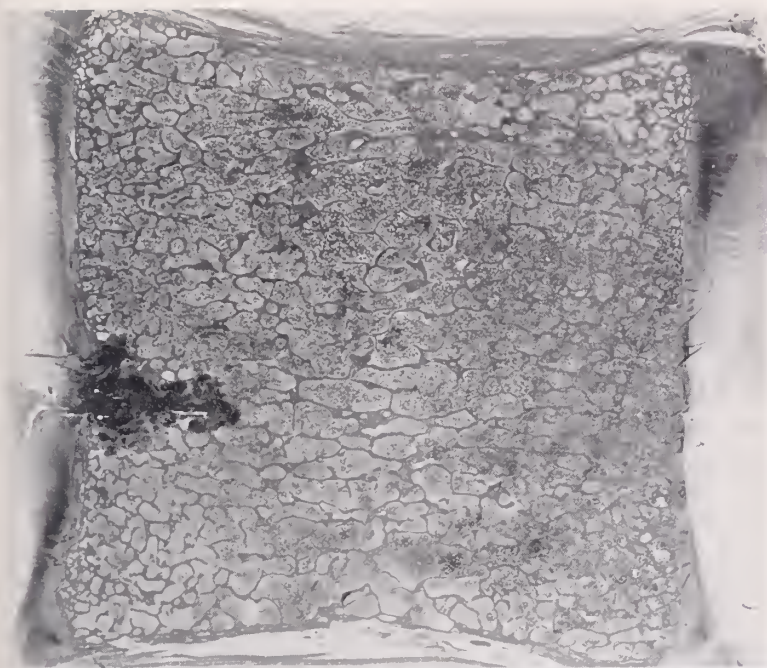


FIG. 35

Figure 44. 65 year old female. Note the marked decrease in cellularity and widespread areas of avascular degeneration characteristic of all senescent tissues, but made particularly visible in bone preparations.



FIG. 36. 34 year old male. Adult specimen. The lower part of this plate exhibits a particularly clear view of an adult intervertebral nucleus.

Figure 45. 74 year old male, and Figure 46. 72 year old male. These figures are chronologically reversed in order better to demonstrate a characteristic development in the senescent vertebra. In the former, note a light ossification reaching into the anterior longitudinal ligament from the adjacent margins of the vertebral bodies. In the latter specimen note the advanced state of ossification of these



FIG. 37. 43 year old male. Adult specimen. Note the large degree of concavity of the anterior and posterior surfaces in this section. It is not abnormally curved however and represents merely a variation in contour.

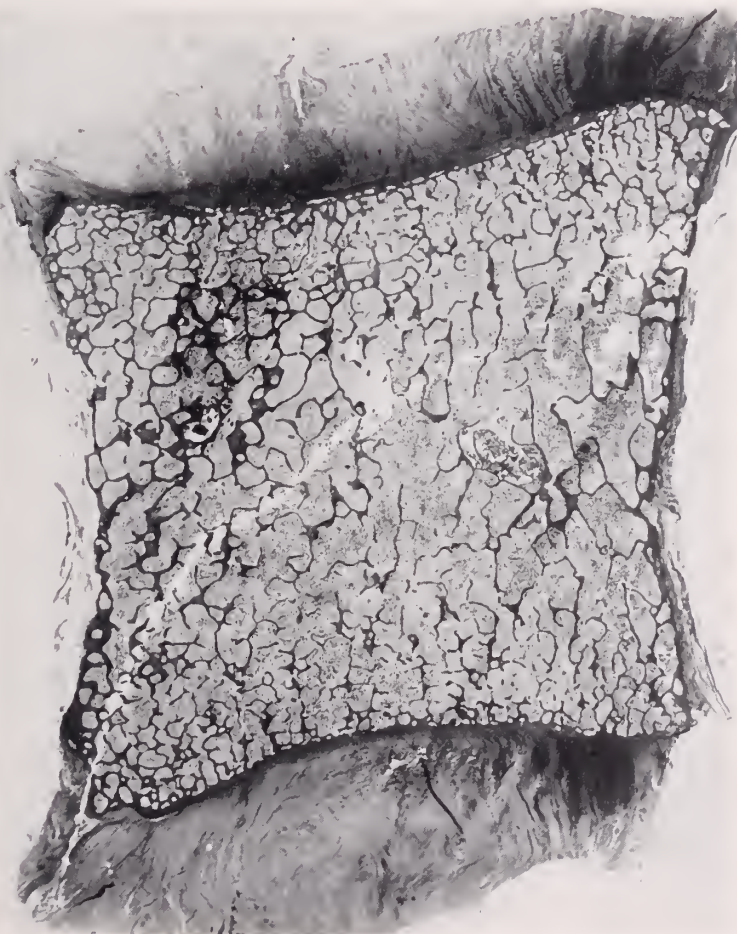


FIG. 38. 48 year old female. The female adult specimens do not differ in any histological feature from the male.

processes forming a so-called bridge across the intervertebral space. These are unusual histological sections of vertebral osteophytes, so commonly seen on x-ray films. It is not merely calcification of the ligament. It is a reactive osteogenetic process growing into the ligaments from adjacent bone surfaces. These may be found in early or middle adult life under a variety of circumstances, but are the normal response to the softening, and therefore the anti-gravity and postural traumata of senescence. Except in the broadest use of the term, they are not in themselves manifestations of arthritis considered as a disease process. The descriptive term *senile osteophytosis* seems more suitable. Whether such appear-



FIG. 39. 48 year old male. Adult specimen. This section shows rather strikingly the predominance of vertical trabeculae.

ances are to be considered pathologic or not depends upon one's conception of the term senescence. (Cf. *Figure 50*.) Vertebral osteophytosis, in this age group at least, is certainly to be classified among the common variables in otherwise normal senescent specimens.

Figure 47, 80 year old male, and *Figure 48*, 36 year old male. These two figures should be viewed together. Both have been stained by the van Giesen method, while all other figures in the *Atlas* are haematoxylin-eosin stained. The van Giesen stain emphasizes the trabecular matrix in bone, chiefly composed as it is of a collagen-protein complex. In *Figure 47* the characteristic sparsity of the trabeculae in the aged vertebra is clearly demonstrated, as compared to the typical adult specimen of *Figure 48*. The persistence of the relative predominance

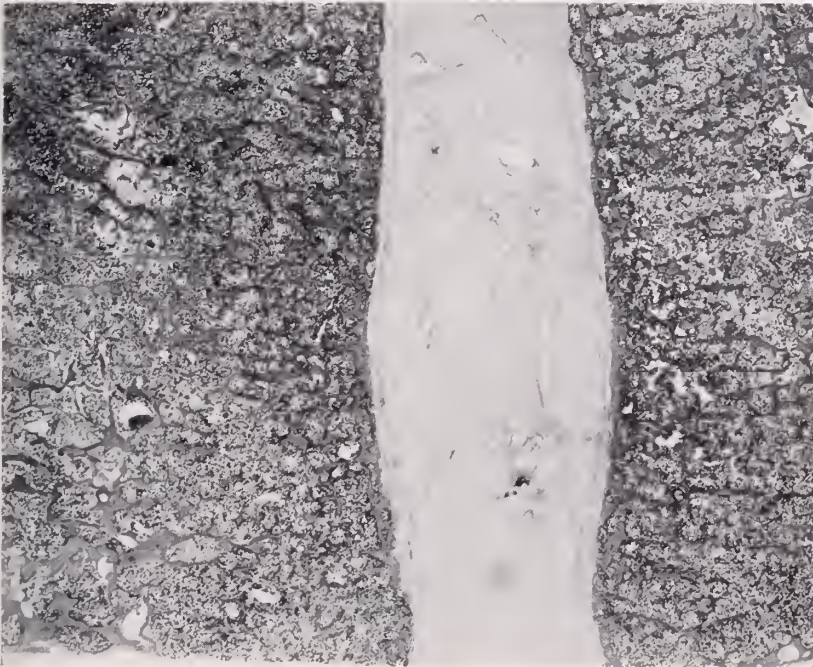


FIG. 40

FIG. 40. 50 year old male. Note particularly in this adult specimen the histological solidity of the intervertebral tissue.
 FIG. 41. 52 year old female. There is still no noticeable histologic difference between male and female sections. (This repeated statement is discussed in the text.)

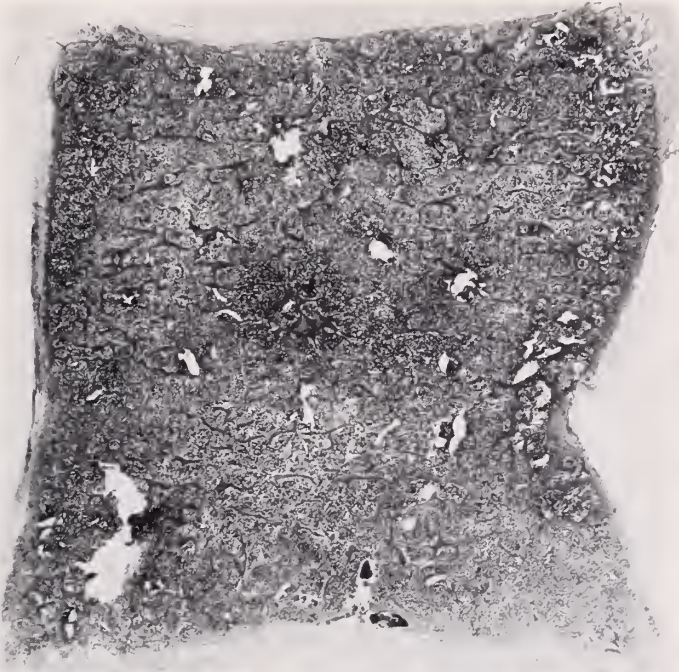


FIG. 41

of vertical trabecular lines is especially noticeable at both extremes of life, and is well shown by this staining method. (Cf. *Figure 6*, three day old specimen.)

Figure 49. 85 year old male. Areas of avascular degeneration are particularly clear. The dense cellularity is composed chiefly of red cells extravasated into the marrow spaces. In this specimen, note the persistence of the squared off structure of the vertebral body in spite of advanced histological senescence which should invite compression.

Figure 50. 90 year old female. This section exhibits all of the characteristics of the internal architecture of bone in advanced senescence described above, except that no reactive osteophytosis has taken place at the vertebral margins.

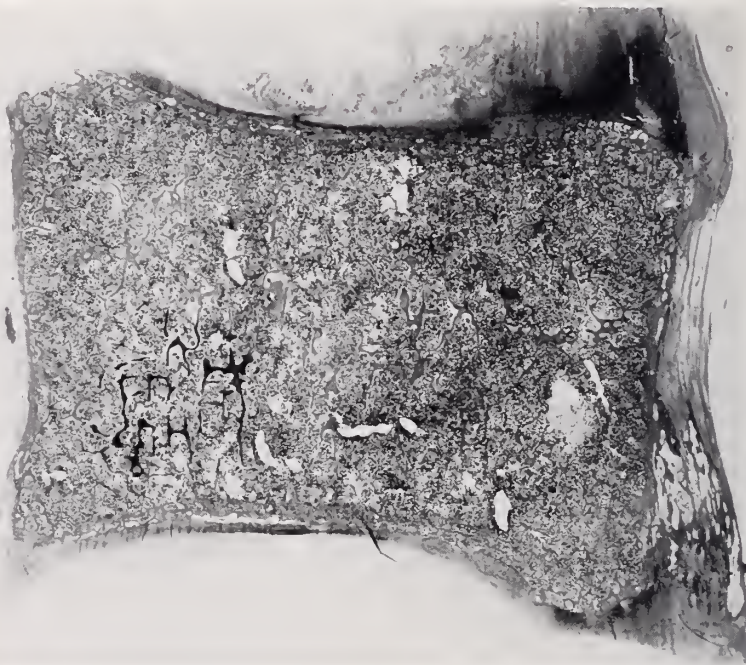


FIG. 42. 58 year old female. This is the last of a sampling of eleven adult normal specimens showing the ordinary histologic variations found among a group of such sections.

GENERAL COMMENT

It is most difficult to summarize the direct observations recorded in these fifty specimens. Matters of histologic interest were discussed in the legends referring to specimens in which they were demonstrated or, in several instances, in references to a group of related specimens. However, certain anatomic and clinical implications inherent in a review of the series perhaps merit special consideration.

1. The anatomic form of the vertebral body is fixed by soft mesenchymal derivatives long before it is ossified. Only the superficial details of its structure are influenced by the antigravity pressures and tensions of active life in the normal



FIG. 43

FIG. 43. 62 year old male. Senescent vertebra. Note the decrease in trabecular density and the diffuse signs of osteoporotic and avascular involution.



FIG. 44

FIG. 44. 65 year old female. Note the further decrease in cellularity and trabecula density. The involutional changes are characteristic if senescence in all tissues but are perhaps more striking in bone.



FIG. 45

FIG. 45. 74 year old male. Note the light area of ossification reaching into the anterior longitudinal ligament from adjacent margins of the vertebral bodies. This process is also a characteristic response of vertebral bone to senescence. Such protrusions form the substance of osteophytosis of the spine.



FIG. 46

FIG. 46. 72 year old male. This unusual and important section is from a specimen two years younger than the preceding but is shown in this order because of the more advanced development of its osteophytosis. Note the complete "bridging" of the anterior longitudinal ligament at the adjacent corners of the vertebral bodies. However note also that in both there is a line of demarcation along their transverse mid-way level. This marks the meeting line of two juxtaposed osteophytes.

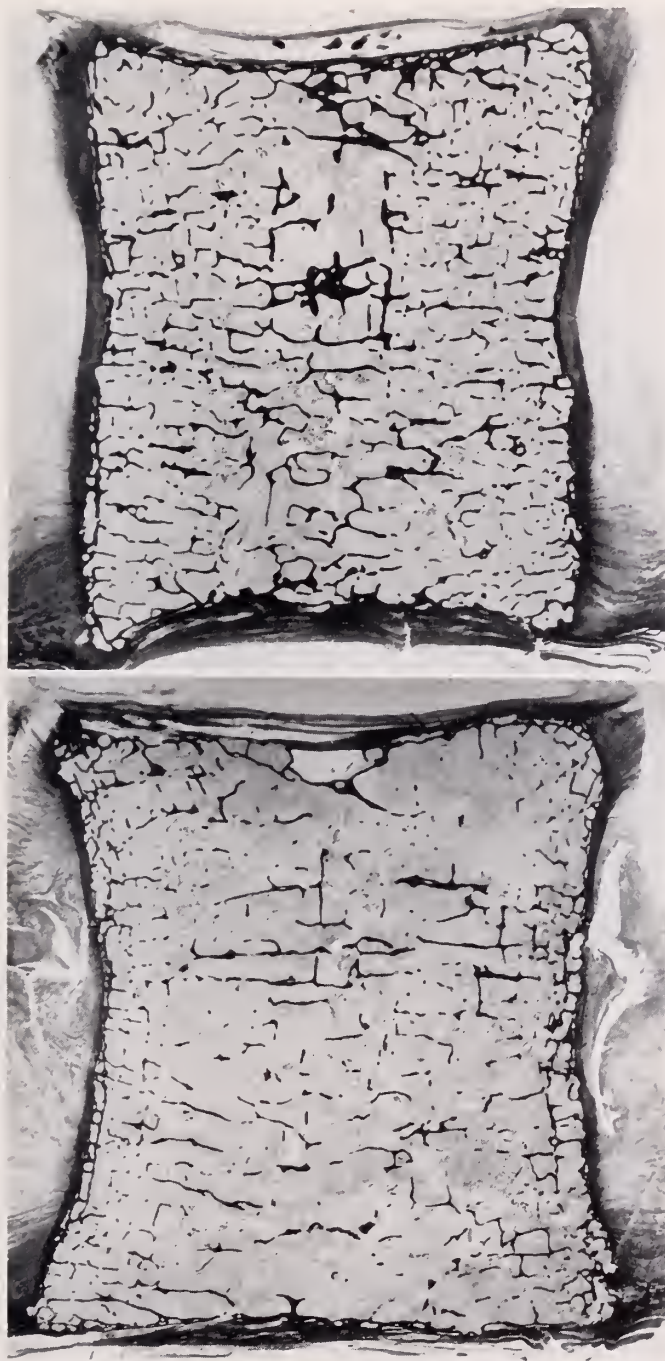


FIG. 48

FIG. 47

FIG. 47. 80 year old male. This Figure is stained by the van Gieson method in order to emphasize the trabecular matrix in bone substance. The characteristic sparsity of trabecular substance in the aged can be clearly seen, especially in comparison with the following Figure.

FIG. 48. 36 year old male. This adult section is inserted here as a comparison with the preceding specimen. It is also stained by the van Gieson method. (All sections other than these two are stained by haematoxylin-eosin.) It serves to emphasize more graphically the difference between adult and senescent vertebral bone in reference to their trabecular thickness and area density.

state. This inherent tendency to adult form is seen again during the early foetal days of ossification when, long before the stresses and strains of anti-gravity forces come into play, the greater relative size and quantity of the bone trabeculae within the vertebral body mass lie in the vertical plane. The implications of this fact may have a bearing on considerations of the development of structural scoliosis.

2. The vertebral body grows longitudinally as does the diaphysis of a long bone of the extremities, but without appended epiphyses (6). Since the columnar cartilage plate of all such bones marks the advance of diaphyseal ossification



FIG. 49. 85 year old male. Areas of avascular necrosis (senescent involution) are particularly clear in this section. In the lower right hand corner is an osteolytic area representing a localized necrotic spot, a bone infarct. Such spots occur in advanced senescence as part of the involutional process.

rather than actual skeletal growth, and since such growth can take place, as in the vertebra, in the absence of an appended epiphysis, the term *diaphyseal plate* is more appropriate than its common misnomer, epiphyseal plate.

3. Since the vertebral body does possess the same diaphyseal plates as do the long bones, they are subject to the same internal or environmental influences.

4. It therefore follows that, if the so-called Hueter-Volkman Law which states in effect that pressure retards and traction accelerates the advance of the diaphyseal plate, is valid, the effect of these forces on the development of structural scoliosis should be demonstrable. Furthermore, the effect of the Hueter-Volkman Law may be reversible during the growth period in the spine, as it is in the long bones.

5. By the same observation, it must follow that any effect which rickets or other disease imposes on the diaphyseal plates of the long bones of the extremities must be equally operative on those of the vertebrae.

6. Since the peripheral ring of the cephalic and caudal surfaces of the vertebral body, commonly but erroneously referred to as the vertebral epiphysis, meets rather the requirements by definition of a traction apophysis, and fails to meet those of an epiphysis, lesions ordinarily operable only on epiphyseal structures



FIG. 50. 90 year old female. This final section exhibits all of the characteristics of advanced senescence in the vertebra described in preceding sections except that no reactive osteophytosis has taken place at the points of insertion of the anterior longitudinal ligaments.

cannot properly be ascribed to those found in this structure. This one, therefore, has been more suitably termed the *vertebral ring apophysis* (7). The concept of vertebral epiphysitis, applied by his successors to the lesion described by Scheuermann as adolescent kyphosis, is therefore physiologically untenable and requires reevaluation. Incidentally, Scheuermann himself considered the lesion to be an effect of avascular necrosis on the body mass of the vertebra.

7. The variation in the osteohistology of the human vertebral body in different age groups is sufficiently marked so as to warrant a normal scale of reference specimens against which early pathologic changes can be measured. This is

particularly apparent in the adult and senescent spine, in relation to osteoporosis, Paget's disease or other lesions which present exaggerations of normal trabecular structure rather than specific pathognomonic cellular aberrations or intrusions.

8. A reference to the progressive and normally varied osteohistology of the human vertebra is essential to a proper understanding of the effect of internal and external mechanical and pathologic influences on the human spine.

My sincere appreciation must here be expressed to Dr. Joseph W. Copel, one time Orthopaedic Resident at The Mt. Sinai Hospital, for his valuable assistance in collecting and preparing specimens for this study, and to Miss Sarah Spector, technical assistant in osteohistology, who devoted more than her required efforts to cutting and staining complete sagittal sections of the vertebral bodies. For permission to use certain illustrations previously published in the *Journal of Bone and Joint Surgery*, I am indebted to its Editor, Dr. Mark Rogers.

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ABSTRACTS

AUTHOR'S ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL, STAFF

Members of the hospital staff and the out patient department of the Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

The Dynamic Nature of Thermophily. MARY BELLE ALLEN. J. Gen. Physiol., 33: 205, January 1950.

Evidence for a close relation between thermophilic and mesophilic bacteria is discussed. It is shown that in the absence of nutrients thermophilic bacteria at 55°C. die as rapidly as mesophilic bacteria, and that enzyme systems of the thermophiles are rapidly inactivated at this temperature. It is concluded that the thermophiles can live at high temperatures because they can synthesize enzymes and other cellular constituents faster than these are destroyed by heat. In order to account for this great synthetic capacity at high temperatures, and for the high minimum temperatures observed for any thermophiles, it is postulated that these organisms have a higher temperature coefficient of enzyme synthesis than mesophiles.

Disappearance of Hyaluronidase from the Blood of Albino Rats. S. K. ELSTER AND E. L. LOWRY. Proc. Soc. Exper. Biol. & Med., 73: 49, January, 1950.

Following the intravenous administration of testicular hyaluronidase to albino rats, the following changes were noted: 1. The maximum concentration of the enzyme was attained within 5 minutes and diminished rapidly, so that at one hour it was no longer detected by turbidimetric methods. 2. Approximately 2% of the hyaluronidase appeared in the urine in an active form. 3. The plasma hyaluronidase inhibitor level was depressed for 8 hours and returned to normal within 24-72 hours. 4. No significant proteinuria resulted.

The Role of Lipid Deposition in Renal Arteriolar Sclerosis. S. L. WILENS AND S. K. ELSTER. Am. M. Sc., 219: 183, February, 1950.

Lipid deposition in the walls of renal arterioles occurs as commonly as it does in the intima of large arteries. It is relatively infrequent and slight in the very young and increases in incidence slowly but progressively with advancing age in non-hypertensive persons. It is somewhat more common in hypertensive or diabetic women than in similar groups of men. There is no difference in sex incidence of renal arteriolar lipidosis in non-hypertensive persons or in whites and negroes. The incidence of renal arteriolar lipidosis is significantly increased in all forms of hypertension except that associated with chronic glomerulonephritis. It is significantly increased in diabetes. It is not increased in renal diseases that are not associated with hypertension. The incidence and severity of renal arteriolar lipidosis is increased in the presence of arteriolar sclerosis, although scanty lipid deposits are frequently found in arterioles that are otherwise unaltered. Evidence is presented that indicates that lipid deposition may be an early and essential feature in the hyalinization and thickening of arterioles observed in protracted hypertension. It is further suggested that elevation of arteriolar blood pressure or increase of the plasma content of lipid are important factors in the deposition of fat within arteriolar walls.

Synthesis and Properties of Spiranes Containing Oxygen Heterocycles. J. D. CHANLEY. J. Am. Chem. Soc., 71: 829, March, 1950.

The preparation and properties of the dl-bis-epoxide of symmetric dicyclohexylethane and of the isomeric 3,4-epoxide of dispiro[dicyclohexane-2,5,-tetrahydrofuran] are described and discussed.

Use of Anticoagulant (Dicumarol) in Preventing Post-Irradiation Tissue Changes in the Human Lung. Preliminary Report. S. H. MACHT AND H. PERLBERG, JR. *Am. J. Roentgenol.*, 63:335, March, 1950.

There is pathological proof that pulmonary and esophageal carcinoma can be sterilized by proper radiotherapy. Death frequently followed treatment in 4 to 6 months due to radiation reaction in the lungs. An attempt was made to eliminate this paradox based on experimental evidence of a marked gross and microscopic reduction of untoward radiotherapeutic effects on the lungs of rabbits receiving heparin concomitantly. Cancer of the lung and esophagus was treated by rotational x-ray therapy in conjunction with anticoagulant therapy. Death of the initial case, which is reported in detail, occurred halfway through therapy. The proven squamous cell carcinoma of the esophagus showed almost complete eradication at autopsy. There was no demonstrable radiation effect in the lung or pleura beneath any of the treated parts. Encouraging results in several other cases are presented in an addendum. Details of the anticoagulant and radiotherapeutic regimen employed are included.

Congenital Atresia of Pulmonary and Tricuspid Valves. S. K. ELSTER, *Am. J. Dis. Child.*, 79:692, April, 1950.

The case of a 10 week old white female child is reported, who at necropsy was observed to have atresia of the pulmonary and tricuspid valves. Five similar cases have been reported previously. The pathogenesis of this lesion is discussed. It is not possible to classify this case with those of either fetal inflammatory disease or embryologic maldevelopment.

Sclerosis of the Chordae Tendineae of the Mitral Valve. L. SOKOLOFF, S. K. ELSTER, AND N. RIGHTHAND. *Circulation*, 1:782, April, 1950.

The dimensions and histologic appearance of the second order chordae tendineae of the mitral valve were studied in 200 human hearts that were considered grossly to be free from rheumatic inflammation. Two types of relatively thick chordae were found. The central chordae of the anterior leaflet were thickened in all hearts, in subjects of all ages, and a similar pattern was found in the bovine heart. This suggests that this finding is a normal developmental phenomenon. Another type of thickening was seen in 11 of 160 adult hearts. This was of much greater extent and was associated with laying down of large amounts of subendocardial collagen. Of the many factors possibly involved in the pathogenesis of this sclerosis, only two are suggested to be of importance: (1) the lesion was not seen in subjects younger than 37 years of age, and age, therefore, plays a role; (2) the predilection of central chordae of the anterior leaflet of the mitral to undergo this change suggests that mechanical factors, stemming from the character of the blood flow in this region, also are involved.

Diagnosis and Treatment of Celiac Disease. Report of 603 Cases. S. V. HAAS, AND M. P. HAAS. *Post-Grad. Med.*, 7:239, April, 1950.

Celiac disease is a definite clinical entity, whether called a disease or a syndrome. It has a characteristic symptomatology, *intermittent diarrhea*, usually retardation or failure of growth and nutrition, pale foul fatty stools, and behavior disturbances ranging from slight irritability to severe psychic aberration. The condition may exist in the presence of an excellent state of nutrition. Although often referred to as a self limited disease, this is only occasionally the case; but it can be cured in practically every case by a specific diet, in which as far as possible polysaccharides are excluded from the diet for a sufficient length of time. The sugars of fresh fruits are the main source of carbohydrates in the diet, and bananas, being exceptionally rich in this form of carbohydrate, are extensively used. Proteins may be used in the form of meat, fish, cheese, poultry etc, and protein milk or its equivalent in which the lactose has been sharply reduced. Contrary to the usual belief, fats are well tolerated. The diet must be rigidly enforced for at least one year before attempting to use other carbohydrates. The prognosis is uniformly excellent by this method of treatment; cure is usually attained in 18 months.

Psychiatric Problems of the Puerperium from the Standpoint of Prophylaxis. L. LINN, AND P. POLATIN. *Psychiatric Quart.*, 24: 375, April, 1950.

Childbirth plays an important role in the development of mental disease. The woman who is most susceptible to postpartum mental disease is recognizable by the fact that her basic personality is often an abnormal one. She is inclined to be shy, seclusive, stubborn and negativistic, frigid in her sexual life, and unhappy in her role as a housewife. Most striking of all is the frequency with which overt symptom-formation is encountered in the history, namely, hypochondriasis, hysterical phenomena, phobias, and depression, including actual psychotic breakdown. The first step in prophylaxis is case finding. For this a careful psychiatric history and a psychosomatic point of view are called for on the part of the obstetrician. Susceptible women should be put under psychiatric treatment as soon as they are recognized pre-natally. Treatment should be continued for many months postpartum. The paradox of obstetrical analgesia is discussed. Analgesia by itself may aggravate the tendency to illness in the psychiatrically-susceptible woman. Obstetrical analgesia in such women is not a substitute for pre-natal psychotherapy. On the contrary, its use enhances the importance of the latter. Infant feeding is discussed from the point of view of postpartum mental disease.

Endometriosis of the Large Bowel Treated with Testosterone. R. H. MARSHAK, AND A. I. FRIEDMAN, 14: 576, April, 1950.

The X-ray findings of a long, constant filling defect with sharp, irregular borders, intact mucosa and fixation of the bowel, when associated with tenderness on palpation comprise a fairly accurate pre-operative diagnosis of endometriosis of the colon. A 34 year old, blonde, married female complained of pain in the left lower quadrant of 3 months' duration with a change in the character of the stools. The past history included dysmenorrhea and sterility. On physical examination the rectovaginal septum was indurated and in the posterior cul-de-sac a small bluish-gray, 3 mm. nodule was seen. Barium enema examination demonstrated an irregular lesion in the lower sigmoid with an intact mucosa and abrupt convex margins. Biopsy of the nodule confirmed the impression of endometriosis of the rectosigmoid. Three hundred milligrams of Testosterone were given weekly for 8 weeks following which all her symptoms disappeared. In 1945 a cholecystectomy for cholelithiasis was performed. Palpation of the rectosigmoid revealed only slight thickening of the bowel. A barium enema 4 years later was entirely negative.

The "Two-Step" Exercise Electrocardiogram in Functional Heart Disturbances and in Organic Heart Disease: The Use of Ergotamine Tartrate. A. M. MASTER, L. PORDY, J. KOLKER, AND M. J. BLUMENTHAL. *Circulation*, 1: 692, April, 1950.

Patients with functional cardiac disturbances, including chest pain, may present electrocardiographic abnormalities (pronounced RS-T depressions and T-wave inversions) after the "2-step" exercise test which are indistinguishable from those found in organic heart disease. Ergotamine tartrate was employed intravenously in conjunction with "2-step" tests in 10 cases for the objective differentiation of functional from organic heart involvement. However, ergotamine was found to be contraindicated as a routine for this purpose because of its anginal-provoking properties. We have substituted dihydroergocor-nine (DHO-180), a newer, safer ergot alkaloid, in our further investigation of this problem.

Sensitivity Reactions to Aureomycin. S. M. PECK AND F. F. FELDMAN. *J.A.M.A.*, 142: 1137, April, 1950.

Three patients with allergic skin eruptions due to aureomycin are reported. One eruption was urticarial in type. The second presented an erythema multiformelike eruption and urticaria. The third was an eczematoid eruption in the groin and on the scrotum of the type usually seen after administration of penicillin. Scratch and intradermal tests as well as patch tests with aureomycin failed to elicit a positive reaction.

A Quantitative Method for the Determination of Antihistaminic Compounds Containing the Pyridine Radical. ELY PERLMAN. J. Pharmacol & Exper. Therap., Vol. 95, No. 4, April, 1949.

A fluorometric method suitable for the determination of a number of available antihistaminic compounds is described. The addition of cyanogen bromide to these compounds results in a new substance which exhibits an intense blue fluorescence when exposed to ultraviolet light. It was found that fluorescence develops only with those antihistaminic substances which contain the three nitrogen atoms in the same configuration as found in Pyribenzamine.

Those antihistaminics which contain the pyridine radical only, develop a color which can be intensified with coupling agents such as p-aminoacetophenone. The test was applied to a study of the urinary excretion of Pyribenzamine from patients receiving this medication. No free bases were obtained when such urines were made alkaline and extracted with organic solvents. It was found, however, that if such urines were heated with alkali, material could then be extracted with organic solvents which would develop a fluorescence with cyanogen bromide. This material appears to be Pyribenzamine in view of the fact that it could be precipitated as the picrate with the same melting point as Pyribenzamine picrate, and mixed crystals exhibited the same melting point. It was further shown that the isolated material had antihistaminic activity by pharmacological test. The material was also studied at three values of pH in the Beckman ultraviolet spectrophotometer and was found to have identical maxima, minima and isobestic points as found for Pyribenzamine itself. This method was applied to a study of the rate of excretion of single doses of Pyribenzamine in patients' urine. About 10 per cent of the ingested dose is excreted in 24 hours and intravenously administered Pyribenzamine is excreted at the same rate and to the same extent as the same dose taken orally.

Cardiac Arrhythmia in Dextrocardia. B. RICHMAN. New York State J. Med. 50: 1009, April, 1950.

Two cases of dextrocardia with nodal arrhythmia were presented: Case 1 consisted of a regular sinus rhythm with occasional nodal ectopic beat. Case 2 consisted of an arrhythmia known as reciprocal rhythm. It may be seen in nodal, idioventricular rhythm with premature ventricular systole, or in some cases of paroxysmal ventricular tachycardia. In this arrhythmia the nodal or ventricular beat has a retrograde P wave which is followed by another ventricular complex, provided the RP interval is prolonged to 0.2 second or longer. Following this interval the ventricles are in a non-refractory phase and a response is elicited. This must be differentiated from pseudoreciprocal rhythm which occurs in sinoauricular block with nodal escape in which case the P wave resembles the other sinus P waves and uniformity of the PP interval.

Obstetrical and Gynecological Aspects of Proctology; Review of Literature with Comments. R. TURELL. Obst. & Gynec. Survey, 5: 159, April, 1950.

The proctologic disorders that may be encountered in the fields of obstetrics and gynecology are described. This review is based on the literature of the past 5 years as well as on personal observations and management of some of these lesions.

Uses of Radioactive Isotopes in Medicine. L. R. WASSERMAN AND R. LOEVINGER. Adv. Int. Med., 4: 77, April, 1950.

The monograph presents a condensed, systematic review of the radioisotopes in medicine, beginning with a discussion of the history and physical aspects of stable and radioactive isotopes. The detection of radioactive isotopes in medical use is discussed under the headings of *in vivo*, *in vitro*, and radioautographic technics. Tracer uses of the isotopes in intermediary metabolism, mineral metabolism, pharmacologic and toxicologic studies, respiratory exchange, and nonmetabolic physiologic studies are presented. The use in therapy and

diagnosis is summarized with a table of all radiosotopes used, and then discussed under the separate headings of the more important elements, phosphorus, iodine, and sodium, radio-colloids, and other elements. A brief discussion of radioisotope dosimetry in general is followed by separate discussions of dosage from beta and gamma radiations. Tables are included which give appropriate physical properties of isotopes of interest in medicine. The bibliography lists 250 publications, through 1948.

Is the Insulin Test Always Reliable? V. WEINSTEIN, AND F. H. HOLLANDER. *Gastroenterology*, 14: 586, April, 1950.

This is a reply to a recent editorial by W. C. Alvarez in "Gastroenterology" concerning the insulin test and its use in cases of vagotomy for peptic ulcer. The question was posed as to whether this test is the best or only test for completeness of vagotomy. The present comment discusses the advantages of acidity determinations over motility studies, "psychic secretion" tests, and clinical findings as indicators of the presence or absence of gastric vagal continuity; also the necessity of using insulin hypoglycemia as a vago-centric stimulus because no other pharmacologic agent is currently available for this purpose. It is restated, however, that the insulin test can not predict clinical efficacy of the operation on ulcer patients. It has been repeatedly recommended only as an investigative tool for determining the completeness of vagal section in the many research problems concerned with the operation.

Effects of Increased Pressure upon Sarcoma 180. ALVIN M. ARKIN, AND KANEMATSU SUGIURA. *Cancer Research*, 10: 272, May, 1950.

In line with clinical observation that increased pressure inhibits tumor growth, experimental confirmation was obtained by subjecting sarcoma 180, a transplantable mouse tumor, to various types of pressure. It was found that any type of pressure would result in inhibition of tumor growth. Thus tumor growth was inhibited if the entire animal was compressed in a pressure chamber under compressed air conditions. This was a true pressure effect and not due to variations in partial pressures of oxygen. Better results were obtained when the tumor alone was compressed by implantation into the firm tissue of the tail. Under these latter conditions a large number of spontaneous regressions was observed. It is suggested that this behavior depends upon the fact that the synthesis of a given quantity of protein out of an equivalent amount of constituent amino-acids is accompanied by a volume increase. Any chemical reaction accompanied by a volume increase is inhibited by increased pressure.

Considérations générales sur les préparations de cavités d'inlay du point de vue bio-fonctionnel. (General Considerations on Inlay Cavity Preparation from a Bio-Functional Point of View). E. BADEN. *L'Inform. Dent.*, 21: 1009, May, 1950.

Following a study of the direct and indirect methods of inlay construction and analysis of the advantages, disadvantages, indications and contra-indications of inlays, the author studied the fundamental principles of cavity preparation from a bio-functional point of view. The importance of thorough diagnosis including consideration of the age of the patient, the medical and dental history, the psychologic attitude of the patient as well as the evaluation of the vitality of the tooth to be prepared, the occlusion, the access, the extent of carious destruction and the radiographic findings are all stressed. The histo-physiology of the tooth is studied from the point of view of cavity preparation. As the tooth participates in the metabolism of the body as a whole, the knowledge of sound anatomical, physiological, histologic and bio-chemical basic concepts of the dental organ is of paramount importance, for cavity preparation for inlay restoration is a surgical procedure on a living tissue; hence the knowledge of the special biology of the tooth is invaluable to insure proper restorative treatment. Dentin formation, sensory transmission of pain and thermo-irritation, thermo-reaction and surgical reaction of the pulp; the action of chemical and particularly anti-

septics on the dentin and the pulp are studied in detail. The author concludes by emphasizing the close interplay of all biologic factors and the restorative treatment of the tooth. To guarantee satisfactory results a good working knowledge of the bio-functional factors is indispensable.

An Unusual Sensitivity Reaction to Penicillin—Report of a Case With Autopsy Findings.

ROBERT M. BERNE. *New England J. Med.*, 242: 814, May, 1950.

A 53 year-old man was treated for pneumonia with penicillin in oil and wax. Following 2 successive injections of 300,000 units of penicillin the patient developed an erythematous rash, bullae, facial edema and wheezing respiration. These lesions cleared within the next 6 days upon treatment with epinephrine and Pyribenzamine. After a third injection of penicillin the lesions reappeared. The patient then developed generalized edema, exfoliative dermatitis, subcutaneous hemorrhages and a sterile peritonitis which terminated in death 13 days after this last dose of penicillin. Post-mortem examination revealed extensive hemorrhagic and necrotic lesions involving primarily the skin and gastrointestinal tract, the jejunum and ileum being most severely affected. Vascular and perivascular lesions were predominant, the earlier ones showing a greater involvement of the veins than of the neighboring arteries.

Localization Of Cord Tumors By Electromyography. SIDNEY M. COHEN. *J. Neurosurg.*, 7: 219, May, 1950.

Normal striated muscle at rest shows no sign of electrical activity. Pathological stimuli arising at segmental levels due to irritative action on afferent, central or efferent structures, produce muscle action potentials. They can be utilized for the localization of level lesions of the spinal cord. Cord tumor localization by electromyography was attempted in 88 cases with 91 verified lesions. Precise levels were established by this method in 83.1 per cent of 83 lesions considered localizable. In 8 other lesions found at operation or autopsy to be multiple or widespread the electromyographic method had indicated the diffuse nature of these lesions. Electromyography appears to be superior to all other methods employed for localization in our group of cases.

An Appraisal of the Operation of Anterior Resection for Carcinoma of Rectum and Rectosigmoid. JOHN H. GARLOCK, AND LEON GINZBURG. *Surg. Gyn. & Obstet.*, 90: 525, May, 1950.

The authors made a study of the operation of anterior resection for carcinoma of the rectum and rectosigmoid in order to determine the efficacy of the procedure from the standpoint of the incidence of local recurrence and long-term survival. The report is based upon 163 cases which include 128 private patients and 35 ward patients. The operative mortality was 4.6%. The study indicated that when the original growth was situated 3-4 inches from the anus, the local and pelvic recurrence rate was 37.8%. At a level between 4-5 inches from the anus, the recurrence rate was 53%. At the 5-6 inch level, the incidence of recurrence was 20%. At the rectosigmoidal level, namely 6-8 inches, the local recurrence rate was 5.8%. From this extensive study, the authors have reached the definite conclusion that the operation of anterior resection should not be utilized in the treatment of carcinoma of the rectum proper and should be reserved only for tumors located in the rectosigmoid or proximal to it.

A Suggested Modification for the Obstetrical Forceps to Avoid Trauma. EMANUEL M. GREENBERG. *Obstet. and Gyn.*, 59: 1169, May, 1950.

Notwithstanding the many improvements since the introduction of the obstetric forceps, the instrument still takes a high toll in traumatic injuries. To lessen these hazards, the "rubberized forceps" is suggested. Any type of forceps can be rubber cushioned. The blades are first cleaned and dried, then dipped in liquid latex, following special chemical processes.

sing. With proper application and skillful handling the rubberized forceps is less traumatic than the usual forceps, especially during rotation. The rubberized forceps offers more friction, which tends to prevent slipping of the blades.

Electroencephalographic Findings in Measles Encephalitis. H. HODES AND S. LIVINGSTON. J. Pediat., 36: 577, May, 1950.

Eight patients with measles encephalitis showed abnormal electroencephalographic findings soon after onset of their central nervous system disease. In seven of these, the electroencephalographic pattern became normal and all of these children appear to have recovered without detectable evidence of permanent central nervous system injury. In the case of the eighth child, the central nervous system damage did not improve, the electroencephalogram remained abnormal, and death resulted. Six children who were convalescent from uncomplicated measles all showed normal electroencephalograms.

Sulfadiazine and Sulfamerazine in Combined Sulfonamide Therapy. THOMAS G. KANTOR. New York State J. Med., 50: 1237, May, 1950.

Of 32 patients treated with combined sulfadiazine and sulfamerazine, 4 or 12 per cent showed crystalluria and 5 or 3.3 per cent of 151 urines showed crystals. This compares well with figures of other series using sulfa combinations and is much better than those using single sulfas with or without the usual doses of alkali. It has the advantage of requiring dosage every 6 hours rather than every 4 hours to maintain an average blood level of 9.7 mgm. per cent. A group of 14 cases showed that this combination compared favorably with penicillin in the treatment of bacterial pneumonia. The optimum oral dose used was 2 gms. of each drug initially and a maintenance dose of 0.5 gm. of each every 6 hours will also maintain blood levels established by intravenous sulfa.

Effect of Vitamin C Deficiency on the Diffusion of T-1824 Across the Capillary Wall. S. K. ELSTER AND J. A. SCHACK. Am. J. Physiol., 161: 283, May, 1950.

The blue dye T-1824 was administered intravenously to 35 scorbutic and 40 normal male guinea pigs. There were no qualitative or quantitative differences in the tissue distribution of the T-1824, except for the extravasation of the dye into the periarticular soft tissues in the scorbutic, but not in the control animals. The plasma concentration of T-1824 of scorbutic animals was not significantly different from that of normal guinea pigs of the same age, but was significantly less than that of animals of the same weight. The blood hematocrit was not appreciably altered in scurvy. It may be concluded that capillary permeability and blood volume were not altered by vitamin C deficiency in the guinea pig.

On the Effect of Amino Acids on a Color Reaction of Aromatic Amidines. F. LIEBEN. Exper. Med. & Surg., 8: 247, May, 1950.

The violet red color reaction of aromatic diamidines with glyoxal and borate buffer pH 9.0 is increased by addition of α -amino acids. The appropriate set-up to observe this effect is described. If the control color as measured in the Klett-Summerson colorimeter, is arbitrarily set at 100, figures like the following are obtained on alpha amino acid addition: histidine 172, beta-phenylalanine 132, tyrosine 143, glutamic acid 135, cystine 142, glycine 132, etc. Other compounds like creatine, taurine, urea, guanidine, etc. give lower readings (110-120); beta-alanine gave 100. The color tests show a fluorescence, which is likewise increased by addition of alpha amino acids.

Quantitative Determination of Stilbamidine and 2-Hydroxystilbamidine in Urine and Tissue. F. LIEBEN AND I. SNAPPER. Exper. Med. & Surg., 8: 357, May, 1950.

For determination of stilbamidine in urine, the fluorimetric method of Saltzman (J. B. Ch. 168: 699, 1947) was used. For determination of stilbamidine in organs, the tissues are

extracted with one per cent acetic acid. The extract is adsorbed on a Decalso column and eluted with 4*N* HCl + alcohol 95% (1:1). In the eluate the stilbamidine is determined fluorimetrically. The weakly reddish fluorescent 2-hydroxystilbamidine in urine is determined by adsorption on a Decalso column and elution. To the eluate 10*N* Na OH and an alcohol-ether mixture (9:1) is added; a strong yellow fluorescence develops which again can be measured fluorimetrically. 2-hydroxystilbamidine in organs is extracted, adsorbed and eluted just as stilbamidine; to the eluate glyoxal, benzaldehyde, 10*N* Na OH and the alcohol-ether mixture are added and the yellow fluorescence is measured as above. All these methods give only estimates of the amounts of diamidines present.

Multiple Carcinomas of the Large Bowel. R. H. MARSHAK, Radiology, 54: 729, May, 1950.

Multiple carcinomas of the colon are not uncommon. Various authors report an incidence varying from 2 to 3.5 per cent. This is a case report of a female, age 42, with a history of diarrhea and bleeding of 6 years duration. Barium enema examination revealed an irregular constricting lesion in the sigmoid, a small punched out filling defect immediately above this area and 2 additional constricting lesions, one in the proximal descending colon and the other in the distal transverse colon. Fluoroscopically another constricting lesion was seen in the ascending colon. The impression was multiple carcinoma of the large bowel which was confirmed by operation. A resection of practically the entire bowel was performed. Pathologically every lesion was a carcinoma. There was no evidence of any benign polyps. The possibility of multiple colonic lesions should be considered when performing a barium enema examination.

The Two-Step Exercise Electrocardiogram: A Test for Coronary Insufficiency. A. M. MASTER, Ann. Int. Med., 32, May, 1950.

The diagnosis of heart disease is often complicated by the fact that objective evidence of organic disease cannot be obtained. Physiologically, electrocardiographic indications of coronary insufficiency are more likely to become evident in tracings made following exercise than in those made when the patient is resting. The "2-step" exercise test obtains the response of the heart to effort and the status of the coronary circulation can be determined by this exercise electrocardiogram. Coronary insufficiency is practically excluded if two tests are negative, a standard and then a double "2-step." Coronary insufficiency exists if the electrocardiogram following the "2-step" exercise is positive. In a patient with anginal syndrome exercise tolerance may be the only objective evidence of myocardial impairment.

ERRATUM

In the article by Hans F. Häusler and Heinz Sterz on "Zur Frage der Übertragung Sensibler Impulse in Rückenmark des Frosches", which appeared in the Pick Anniversary number of the Journal of The Mount Sinai Hospital, Volume XIX, Number 1, May-June 1952, on pages 124 and 127, in the legends of the illustrations 1, 2, 8, and 9, the "mg." should read "μg."

BOOK REVIEW

Diagnostic Electroencephalography. By HANS STRAUSS, MORTIMER OSTOW AND LOUIS GREENSTEIN, New York, Grune and Stratton, 1952, 296 pages, 46 illustrations. Price \$7.75.

It is just about 15 years since the electroencephalograph has emerged from the laboratory of experimental neurophysiology and experimental psychology to become a diagnostic tool of considerable clinical value. An abnormal electroencephalogram means brain disease and serial electroencephalograms can indicate with a considerable degree of precision the direction and rate of change of the disease process. The diagnostic evaluation of the convulsive state is incomplete without an electroencephalogram which can help distinguish between the symptomatic epilepsy and the congenital or idiopathic epilepsy. The electroencephalogram, properly performed and properly interpreted, can correctly lateralize (supratentorial) brain tumor in about 90% of cases and can localize it with a fair degree of precision in 75% or 80% of cases.

This volume is a systematic descriptive text in contrast to most previous volumes on the subject which have attempted to be atlases or collections of essays. The subject is considered under three general headings: general considerations; disease entities; and diagnostic evaluation of the electroencephalogram. A relatively simple system of classification is introduced which makes unnecessary long detailed descriptions of records, facilitates comparison of data among different laboratories, and permits convenient filing and indexing of records for research purposes. The student of electroencephalography will find clear and simple instructions for all phases of practical electroencephalography including placing electrodes, taking the record, reading the record and writing the report. The authors emphasize that properly the report should consist of three parts: a description of the record; an interpretation of the findings in terms of disturbance of brain physiology; and finally a discussion of the clinical implication of the physiologic disturbance inferred.

The data presented to the reader are derived from two sources. The first is a survey of the large electroencephalographic literature up to the date of publication. The published data are compared with data accumulated at the electroencephalographic laboratory of the Mount Sinai Hospital during the past 10 years. Forty-six illustrations are provided to demonstrate the principles of classification. Because of great variation in phase and distribution of disease process, it is ordinarily impossible to illustrate every type of electroencephalogram obtained in every neurologic entity. The system of classification presented by the authors makes this task quite superfluous since both the electroencephalogram and the disease process are discussed in terms of distribution and nature of physiologic disturbance of the brain. One fortunate result of this type of approach is that it becomes possible to delimit the areas in which the electroencephalogram is useful as well as the areas in which the electroencephalogram is not useful.

An unusually full description of the relation between electroencephalography and mental illness is given. The relation of electroencephalographic changes to normal psychic function as known at the present time is surveyed. All of the relevant literature about the electroencephalogram and the various psychiatric illnesses is summarized and evaluated.

This book is recommended as a reliable systematic descriptive exposition of electroencephalography for the electroencephalographer as well as for the neurologist, the psychiatrist and any other medical man having occasion to call upon it as a diagnostic tool.

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CONTENTS

	PAGE
A SUMMARY OF EXPERIMENTAL EVIDENCE RELATING LIFE STRESS TO DIABETES MELLITUS. <i>Lawrence E. Hinkle, Jr., M.D. and Stewart Wolf, M.D.</i>	537
PHYSIOLOGICAL CONSIDERATIONS OF EDEMA. <i>Marvin F. Levitt</i>	571
SOME THEORETICAL AND PRACTICAL ASPECTS OF THE USE OF FOLIC ACID ANTAGONISTS IN HUMAN NEOPLASIA. <i>Ezra M. Greenspan, M.D.</i>	583
TRIFACIAL (TRIGEMINAL) NEURALGIA WITH EMPHASIS ON ATYPICAL FORMS. <i>Ralph Howard Brodsky, D.M.D. and Norman A. Cranin, D.D.S.</i>	596
ELECTRON MICROSCOPY AS APPLIED TO CARDIOLOGY. <i>Bruno Kisch, M.D.</i>	606
ABSTRACTS.....	612

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A SUMMARY OF EXPERIMENTAL EVIDENCE RELATING LIFE STRESS TO DIABETES MELLITUS*

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Up to the present, no generally acceptable formulation of the meaning and etiology of diabetes mellitus in humans has been available. Although the disease occurs in some persons in whom the Islets of Langerhans have been destroyed, and in some others who have tumors of the pituitary or the adrenal cortex, these are but a tiny portion of the diabetic population. Because of the frequent association of obesity with diabetes it has been suspected that obesity predisposes to diabetes, although it is equally tenable that obesity may be a part of the diabetic syndrome. The frequent occurrence of diabetes in some families and cultural groups has led to speculation that it is inherited as a Mendelian recessive characteristic, but the possibility that it may be related to environmental factors cannot be excluded, since persons who share the same environment are subject to the same life experiences. In short, our present understanding of the disorder provides us with but small indication of which persons are likely to develop diabetes, and no indication whatever of when and under what circumstances.

Diabetes mellitus in humans is a notoriously labile and unpredictable syndrome. It is a common clinical experience that wide fluctuations in the metabolism of patients may occur despite the most careful regulation of their diet, insulin, and muscular activity. Often the clinician is faced with an apparently spontaneous increase in his patient's insulin requirement associated with thirst, polyuria, and ketosis, or an equally unexplained decrease in his insulin requirement associated with episodes of hypoglycemia. It has been established repeatedly that infections, trauma, surgical operations, and a large number of miscellaneous disordered states such as hyperthyroid crises and cardiac failure, may be accompanied by an increase in the insulin requirement. Likewise, some patients with abnormal electroencephalograms may have hypoglycemic attacks which are in part alleviated by anti-convulsant drugs (1). The large majority of the metabolic fluctuations of the labile diabetic, however, occur in the absence of any of these generally recognized factors and make it evident that other factors must be involved.

The possibility that personal conflicts arising out of stressful life situations were germane to the course of diabetes mellitus has long been considered. Following Claude Bernard's experimental production of diabetes in animals by puncturing the floor of the fourth ventricle, the possibility of a "neurogenic" cause for

* Lecture given on March 19, 1952 at The Mount Sinai Hospital, New York, N. Y.

diabetes in man was widely entertained. The concept fell into relative obscurity, however, after Joslin (2) and others were unable to find evidence that there was an increased incidence of diabetes among combat soldiers during the first World War. Later, the isolation of insulin from the pancreas implied for most investigators a purely endogenous or degenerative basis for the syndrome. In the meantime, however, Cannon had demonstrated the occurrence of glycosuria in cats under stress (3), and Folin, Dennis, and Smillie had observed a similar phenomenon in man (4). Many reports appeared in the literature describing exacerbations and remissions of diabetes in association with "emotional trauma" and psychotic episodes (5-14), although most workers in the field attached little importance to this phenomenon. Both Baker (15) and Beardwood (16) noted the occurrence of coma in patients during episodes of "emotional stress." Others also observed the association between stress and the decompensation of the diabetic state, but usually attributed it, as did Rosen and Lidz (14) to the patient's willful abandonment of the prescribed regimen. However, it also became apparent that a mechanism exists by which a diabetic might develop pronounced metabolic fluctuations despite faithful adherence to a previously adequate regimen. The discovery of the diabetogenic effect of the anterior pituitary by Houssay was followed by the elucidation of the importance of the adrenal hormones as well, and later Conn and his collaborators described the appearance of diabetes in humans during the administration of ACTH (17). This work was paralleled by the development of Selye's concept (18) that the pituitary and adrenal were part of a general mechanism through which vertebrates adapt to threats to their integrity. Exposure to cold, exhausting exercise, surgical operations, and similar physical assaults are commonly numbered among the threats or "stresses" which lead to the discharge of anterior pituitary and adrenal cortical hormones; but perhaps the commonest stresses that the human being encounters are symbolic threats concerned usually with problems of interpersonal relationships—words or events perceived by him and consciously or unconsciously evaluated as threatening because of his past experience or conditioning. The present communication concerns an experimental investigation of the effects of stressful words, events, and situations upon some aspects of the glucose and ketone metabolism, and of the fluid balance of normal and diabetic persons.

PROCEDURE

The subjects were patients from the Medical Clinics of the New York Hospital and volunteers from the hospital staff. The patients were average individuals encountered in a diabetic clinic, except that a relatively large proportion of the group were severe and labile diabetics. On each subject a detailed medical history was recorded as well as a physical examination and appropriate laboratory procedures. In addition, a detailed evaluation of his personality structure, life history, cultural background, present life situation, and significant conflicts, was undertaken through a series of interviews. Data were derived from discussion, questioning, associative procedures, dream analysis, social service case study, and psychologic tests. Moreover, the attitudes and motivations of the subject

were assessed by observation of his behavior and reactions, especially during the discussion of difficult life experiences, by things he said and left unsaid, by statements from other members of his family, and so forth. The investigation of most subjects included from ten to as many as one hundred one-hour sessions over a period of from three months to four years. Special note was made of the content of the situations when ketosis or hypoglycemia occurred, their significance to the subject, and his reaction. This inquiry revealed a striking coincidence between the occurrence of stressful life situations and clinical decompensation of the diabetes, the details of which are reported in full elsewhere (19).

Long term studies were made on these persons both in the hospital and in their home environments, by simultaneous observation of such factors as their clinical state, their insulin requirements, their food and fluid intake, their output of water, glucose and electrolytes, and the events and situations in their daily lives. From time to time, short term studies also were made in the laboratory. These experiments were performed in the morning after an overnight fast. (Those diabetic subjects who had been receiving insulin had previously been regulated on a single morning dose of mixed protamine and regular insulin, which was omitted on the morning of the procedure.) Breakfast was omitted also, and the fluid intake of the subject was carefully regulated. He came to the laboratory expecting no more than the familiar "blood sugar test."

Upon the subject's arrival at the laboratory he voided, and a sample of his venous blood was drawn. He was then allowed to sit quietly for about an hour, diverting himself with popular magazines, and second blood and urine samples were obtained. During the next hour he was engaged in a discussion of significant events, attitudes, emotions and life situations which had previously been associated with episodes of ketosis on the one hand or hypoglycemia on the other. Every ten minutes throughout the interview blood samples were obtained from an indwelling venous needle. At the end of the interview a urine sample was obtained, and the patient was strongly reassured and diverted. After a third hour of presumably neutral activity and diversion, final blood and urine samples were obtained. Smoking was not permitted at any time during the three hours.*

The reaction of each subject during the procedure was evaluated by observation of his behavior, including both overt manifestations such as tears, tone of voice, tachycardia, and sweating, and more subtle clues such as slips of the tongue, figures of speech, and fleeting gestures, which gained significance to the observer from his past familiarity with the subject. The statements of the subject during the interview were recorded, and at later interviews the data were supplemented by his conscious recollections and his free associations concerning all three of the experimental hours. This precaution was necessary since it could not be assumed that because he was apparently quietly and contentedly reading

* Extensive control studies were carried out to evaluate the effects of various aspects of the procedures upon the results obtained. Minor changes in posture and activity during the interview were found to have no significant effect upon urinary output. The use of various anti-coagulants and the administration of sodium amytal to a few of the subjects had no effect upon the values obtained for blood glucose or ketones.

a magazine during the control hours he was therefore relaxed and in an emotionally neutral state.

Upon both non-diabetic and diabetic subjects control procedures were carried out which were identical to those described above except that no stressful topics were discussed. It was sometimes more difficult to maintain neutral conditions over such a long period of time than it was to introduce a significant stress. A "blood sugar test" alone may have threatening implications for some diabetics. Furthermore, subjects without breakfast who spend three hours in a laboratory readily become bored and hungry, and often ruminate about their illness and other problems, thereby introducing a stressful stimulus into a control experiment. Therefore, in order to determine whether or not a subject had been in a truly neutral and comfortable state throughout a control procedure it was necessary to ascertain whether or not a direct or symbolic stressful stimulus had been introduced inadvertently by the experimenter or the circumstances of the experiment, and whether or not the subject, through his ruminations, had been reacting to a remembered or imagined stress situation at a time when he appeared "calm and relaxed." Accordingly, subjects for control procedures were studied as carefully before, during, and after the procedure as the subjects who were exposed to stressful interviews, and their experiences were as carefully evaluated.

Blood ketone levels were determined on duplicate samples by the method of Greenberg and Lester (20-22) which in our experience is sensitive within less than 0.3 mg. per cent at levels below 3.0 mg. per cent. A modification introduced in later experiments in an attempt further to minimize the error was the use of a tenfold larger (2 cc.) sample of blood. Blood glucose was determined by one of several methods which respond closely to the "true glucose" content of the blood. Protein-free filtrates were prepared by the method of Herbert and Bourne (23), or by Folin's modification of his original method (24), both of which accurately exclude reducing substances other than glucose. Under the conditions of our studies "normal" values for fasting individuals by this method are 55-80 mg. per cent. Eosinophile counts were made by the method of Thorn et al (25). For blood chlorides the method of Sendroy (26) was used; for blood and urine, sodium and potassium determinations were made with the flame photometer (27). Chlorides in urine were determined by the method of Sendroy (26), and glucose by the method of Benedict (28).

THE BLOOD GLUCOSE

In non-diabetic individuals in a post-absorptive state who were relatively serene and resting, there was little fluctuation in the blood glucose level over a period of three or four hours. However, if the period of fasting was continued for about 16 hours or more there was usually a gradual fall in blood sugar toward a level of 40 to 60 mg. per cent. At about this time there usually occurred a fall in the circulating eosinophiles, a rise in the blood ketones, and an increase in the urinary excretion of water and electrolytes (29). Thereafter, the glucose level ceased to fall, and occasionally rose slightly. This appeared to be a standard response to fasting (fig. 1). It was found that the usual reaction of the non-diabetic

individual to stressful situations arousing anxiety and allied feeling states was an accentuation of this response. Figure 2 is an example of this phenomenon, showing the fall in the blood glucose of a non-diabetic woman which took place during a discussion of her conflicts with her mother. It was observed that this fall in blood glucose was accompanied by a rise in blood ketones and a diuresis similar to that induced by the stress of starvation. In some situations of overwhelming fear or anger, presumably accompanied by the elaboration of epi-

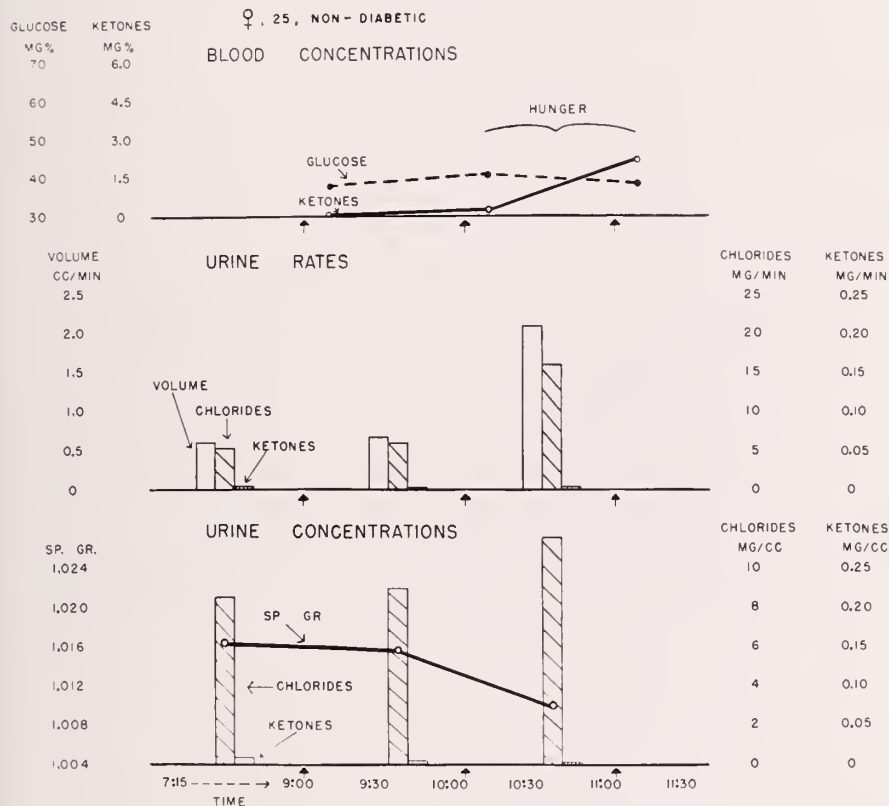


FIG. 1. Four hour observation on a non-diabetic individual who had fasted for 16 hours previously. After the blood glucose had attained a minimal level, a diuresis and rise in blood ketones occurred.

nephrine, a transient rise in blood glucose may occur in normal individuals; but the standard response of the human blood glucose to an acute stress was a transient fall in concentration, which was similar to that observed by Selye in experimental animals.*

The diabetic individual in the post-absorptive state, serene and resting, also showed relatively little fluctuation in his blood glucose concentration, although

* A rise in blood glucose, either in the form of an initial epinephrine hyperglycemia, or of a restoration of normoglycemia after the initial fall during stress, appeared to be a result of the compensatory adaptive processes of the organism.

somewhat more than the non-diabetic. After a period of fasting his blood glucose exhibited a fall, also of somewhat greater magnitude than that of the non-diabetic (fig. 3). It was accompanied by a rise in blood ketones and an increase in the output of water and electrolytes, as well as glucose when that substance

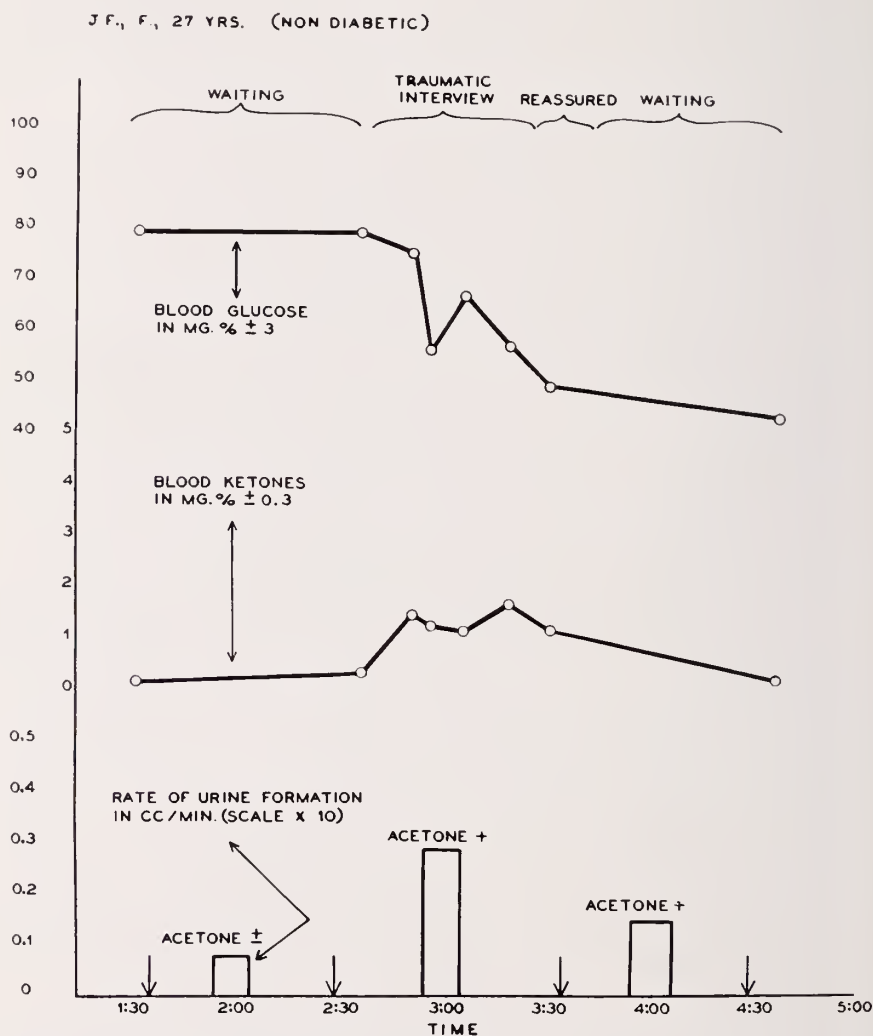


FIG. 2. Fall in the blood glucose concentration of a non-diabetic individual in a stressful situation. A rise in blood ketones and a diuresis occurred at the same time.

was present in the urine (fig. 4). In a stressful situation the reaction of the diabetic subject was also similar to that of the non-diabetic, but of greater magnitude. Usually there was an initial, and sometimes marked, fall in blood glucose, accompanied by increased ketonemia and diuresis (fig. 5). Sometimes the initial fall was compensated for by the adaptive reactions of the subject so that the

original level of glycemia was restored.† In occasional individuals who are overwhelmingly frightened or angry, an initial hyperglycemia at times occurs, and glycosuria may appear even though not previously present (fig. 6). It seems to be characteristic of the diabetic that he maintains his blood glucose with much less constancy in the face of stress than does the non-diabetic. When an individual with "labile" diabetes is presented with a rapidly changing series of threatening situations, his blood glucose level may undergo rapid and profound fluctuations (fig. 7).

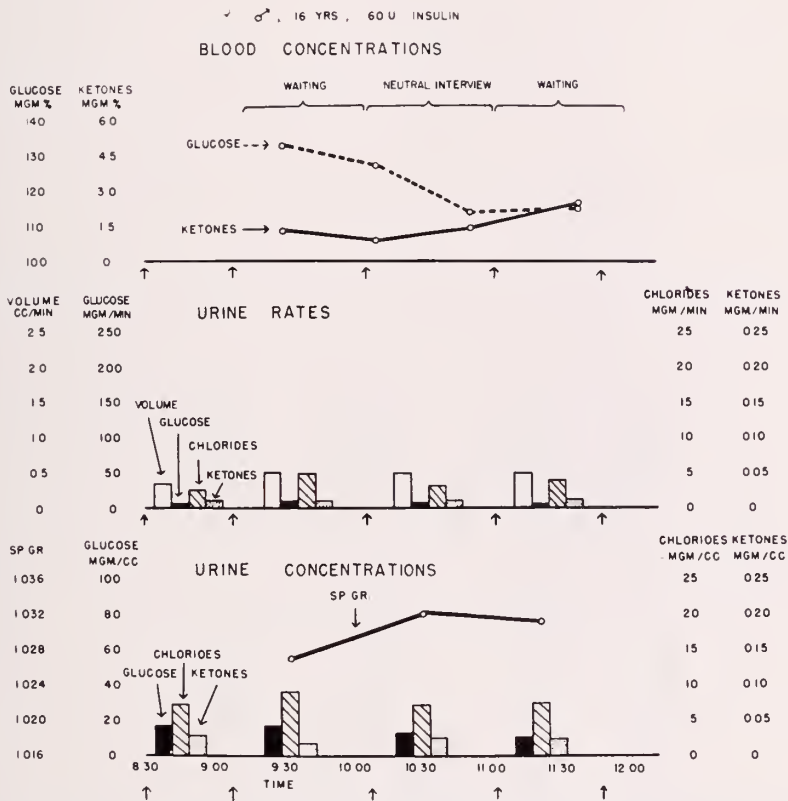


FIG. 3. Fall in blood glucose and rise in blood ketones occurring in a 16 year old diabetic boy after 16 hours of fasting. These observations were discontinued before diuresis developed.

BLOOD KETONES

In many determinations on a large number of healthy, non-diabetic individuals, at times when it could be ascertained that they were under relatively little stress, it was found that the ketone concentration in their peripheral venous

† The very high blood glucose levels often encountered in diabetic individuals during keto-acidosis and coma appear to be a late effect of these adaptive processes, aided and abetted by the patient's continued ingestion of glucose and the cessation of diuresis as he becomes more and more dehydrated.

blood (total ketone bodies expressed as acetone recovered) lay between 2.0 mg. per cent and less than 0.2 mg. per cent, the latter being the lower limit which the method will detect. Most values lay between 1.0 and 0.5 mg. per cent. These levels are in accord with those reported by other workers, including Greenberg and Lester (20), and also by Weichselbaum & Somogyi (30), Crandall (31), Hubbard (32), and Marriott (33), who used various methods of analysis. Some of these workers reported their results as "Mg. per cent of total Ketone Bodies,"

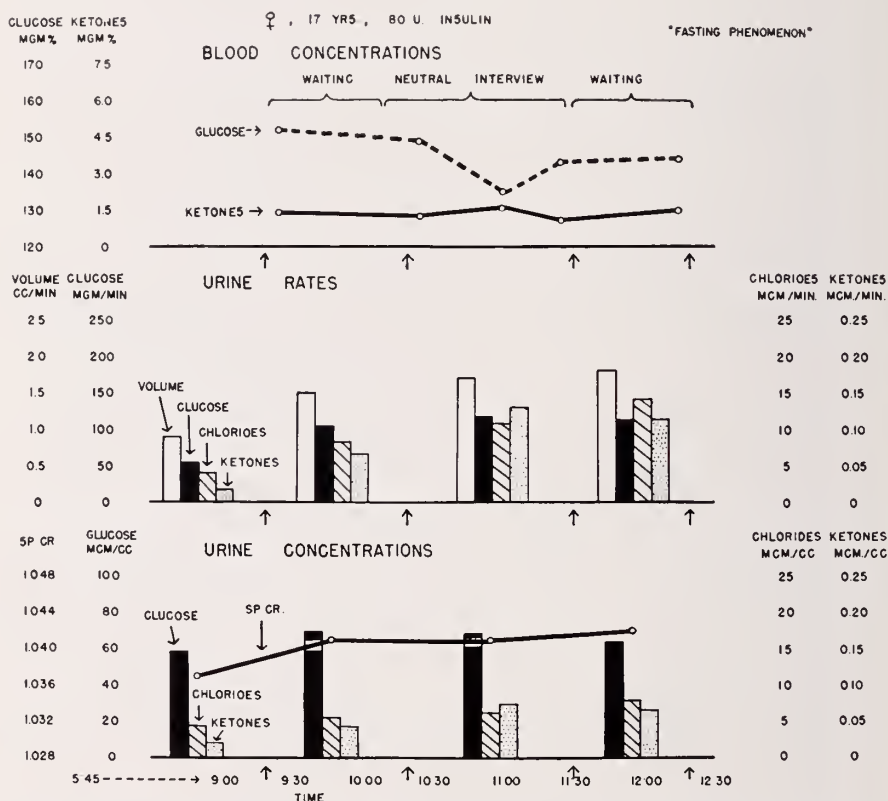


FIG. 4. "Fasting Diuresis" in a Diabetic. Gradual rise in the output of water, chlorides, glucose, and ketones associated with increasing hunger and tension. The increase in glucose excretion occurs in the absence of significant change in the concentration of this substance in blood or urine.

to which our figures may be converted by multiplying by the factor 1.85. We have avoided this method of expression because the exact value of this factor varies according to the proportions of the three ketone bodies present in each sample.

In subjects whose ketones were measured before and one hour after meals, post-prandial falls of from 0.3 to 1.0 mg. per cent were observed. This is in accord with the finding of Somogyi that the blood ketone level falls one to four hours after a meal (34-35).

The results obtained from blood samples of five healthy volunteers are diagrammed in the lower half of figure 8. Their moods, thoughts, and activities were assessed at the time and also reviewed later. All were relatively calm, secure, and happy at the time. The greatest difference between any two consecutive determinations of ketones on one subject was 0.3 mg. per cent, which was also

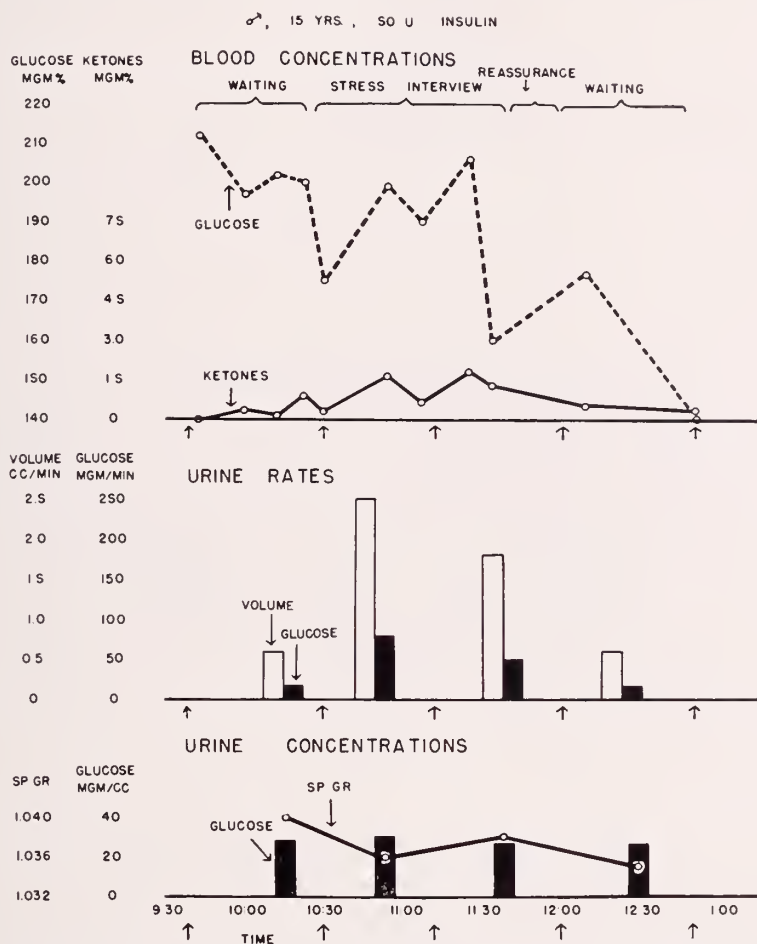


FIG. 5. The effect of a stressful situation on the blood glucose level of a 15 year old diabetic boy.

the greatest difference between any two determinations on the same subject in the same morning. In the upper half of this figure are diagrammed the values obtained from these non-diabetic subjects during stressful situations. In all of the curves, including the controls, the second hour value represents the highest level attained during the interview period, while the other two values were obtained from the first and last samples drawn. It may readily be seen that in all of the persons subjected to stressful situations a rise in the ketones occurred,

and that this was followed by a return to a lower level in those cases in which the stress was subsequently withdrawn. In the control studies, on the other hand, such changes did not take place, and the curves are flat. Thus it appears that a rise in the blood ketone concentration is a usual human response to stress.

In the lower half of Figure 9 are shown the results of control studies on diabetic subjects whose initial blood ketone level was less than 1.5 mg. per cent.

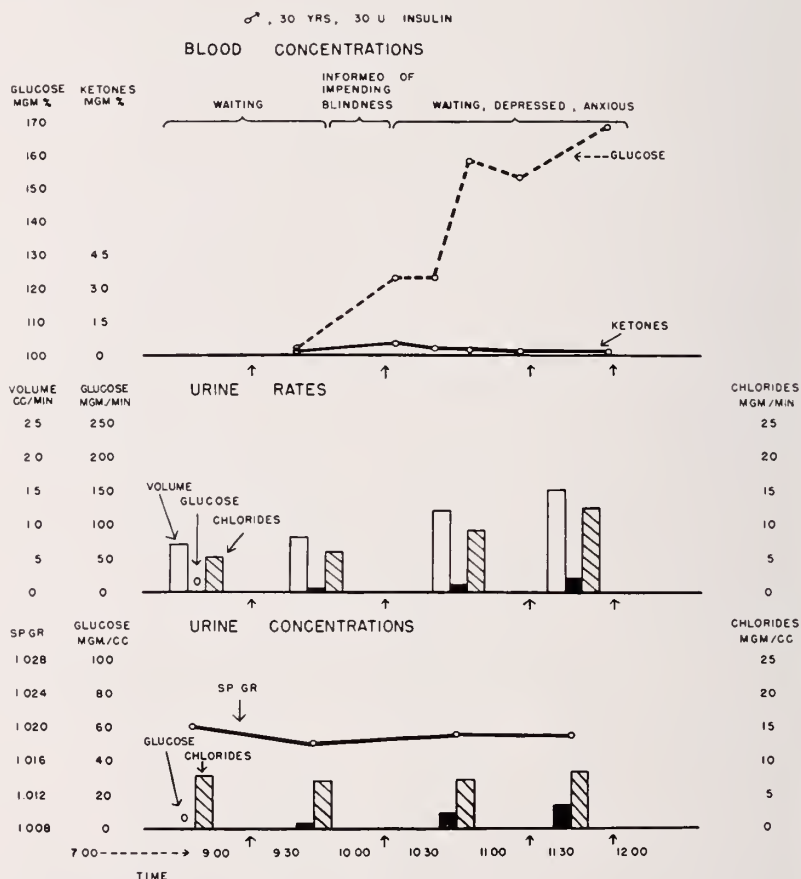


FIG. 6. Hyperglycemia, glycosuria, and diuresis appearing in a frightened man during a period of stress.

This concentration was arbitrarily set as the upper limit of normal under the conditions of our experiments. It may be seen from the diagram that the ketone level of diabetic subjects whose initial level was within this normal range at the outset of the experiment did not fluctuate significantly if it was possible to maintain them in a reasonably comfortable and neutral state throughout a morning. In the upper half of this figure are shown the experimental findings during the emotionally charged interviews in this group of diabetic subjects. In every case the blood ketones rose during the interview and then fell to lower levels when the

stress was withdrawn. It may be seen that in many cases the concentration rose well above 1.5 mg. per cent, returning with reassurance and diversion to levels below this figure. The blood glucose fluctuated widely during the stress procedures, changing as much as 125 mg. per cent in 10 minutes in one subject. In nearly all instances the rises in blood ketone concentration were preceded or accompanied by an initial fall in the blood glucose concentration.

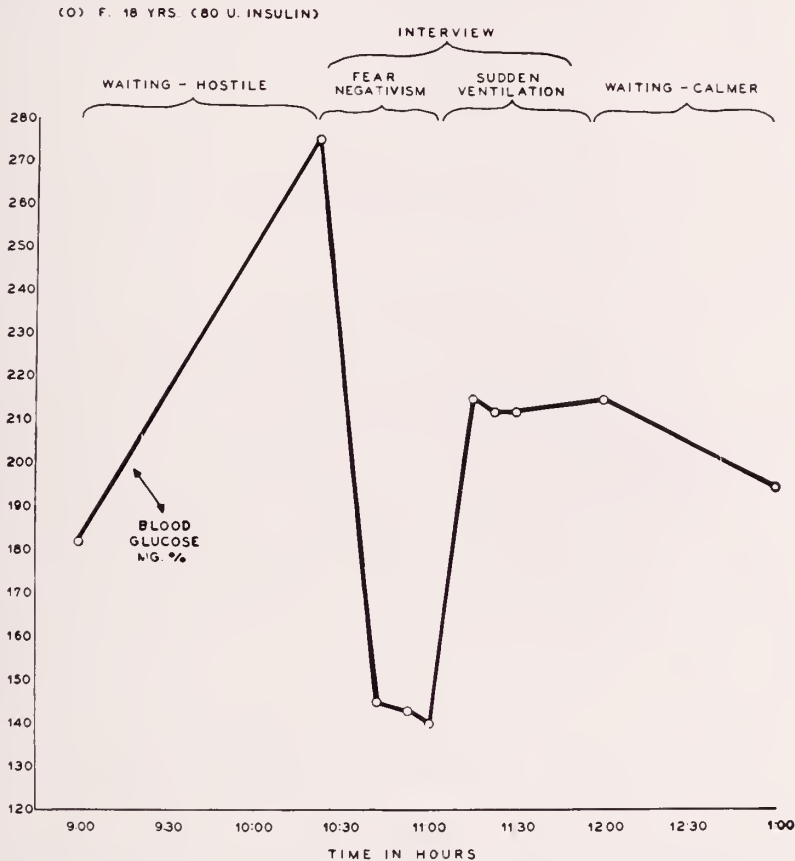


FIG. 7. Fluctuations in the blood glucose level of a girl with labile diabetes confronted with a rapidly changing series of threatening situations.

In individuals whose blood ketone concentration was somewhat elevated at the outset of the procedure, very pronounced rises in blood ketones often accompanied by clinical signs of incipient ketosis could be produced by stress situations. Figure 10 is an example of the effect upon such a subject of being presented with a major threat. When she arrived at the laboratory the physician allowed her to gain the impression that she would be given an injection of sodium amytal, and that she might then be induced to reveal information which she had previously been unwilling to discuss. She was an outwardly innocent, pious girl, but, as revealed in subsequent interviews, the thought that under the influence

of sodium amytal she might disclose her voluminous erotic fantasies aroused intense anger, fear, and guilt within her. These feelings were intensified by reason of the fact that the physician was the object of many of her thoughts. Her conflict persisted with unabated intensity throughout the first waiting hour, and was not dispelled until after the interview had begun, when the words and actions of the interviewer showed her that amytal would not be given after all. Her realization of this coincided with the abrupt fall in ketonemia. After a period of comparatively neutral discussion the topic was turned to her conflict with her

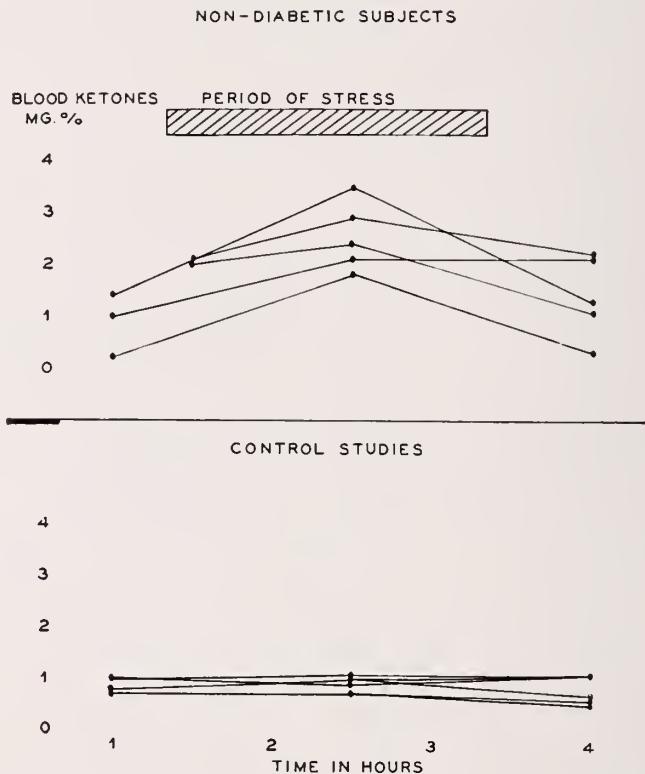


FIG. 8. Non-diabetic subjects: composite graph, illustrating changes in blood ketones during stress (above) and control studies (below).

overprotective, restrictive mother. Again a rise occurred. Finally the physician reassured her of his support and respect for her, turned to neutral topics, and allowed her to divert herself during the last hour. The blood ketones again fell.

On the other hand, the alleviation or removal of a stressful situation was found to produce a fall in the ketone level of persons with an elevated ketonemia. Figure 11 is an example of such an observation. The subject for this study was a boy in whom a rise in ketones from an initial normal level had previously been produced by a stressful interview. He had resented but tolerated the procedure. A month later he was called back peremptorily for a second interview. He was

sullen, resentful and uncommunicative when he arrived, but during the interview he was pleased and relieved to find the discussion limited to model airplanes and sports, two of the chief sources of pleasure in his drab life. When it ended he was smiling, talking freely, and feeling that the physician was an understanding friend. During the last hour of waiting he began to become hungry and bored, but remained much happier than before. There was a steady fall in ketone level

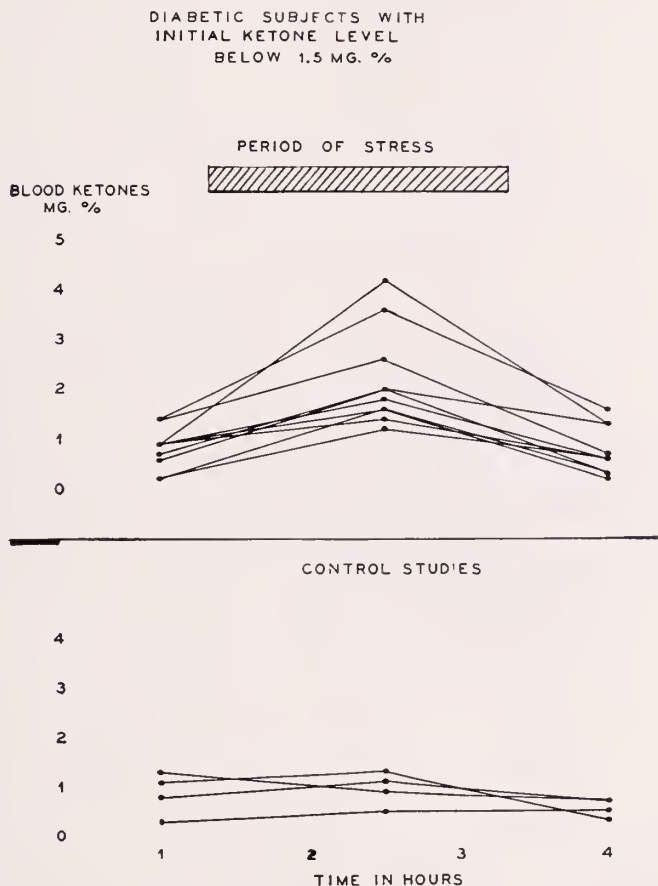


FIG. 9. Diabetic subjects, initial ketone levels below 1.5 mg. per cent, composite graph showing the changes during stress in blood ketones (above) and control studies (below).

during the interview. In another subject, whose blood ketones were 20.8 mg. per cent on arrival, the level fell to 2.0 mg. per cent during a sympathetic and reassuring interview and remained near this value, rising to only 2.5 mg. per cent after the third hour.

It was felt that the changes described in the peripheral venous blood might be related either to ketone production or utilization. Since the liver is known to be the source of the blood ketones, one experiment was carried out while blood samples were obtained from a catheter introduced into the subject's hepatic

vein. Several attempts were made before a suitable experiment could be performed, for it was found that although patients might remain outwardly calm and the true nature of the procedure might be concealed from them, they were all nevertheless aware that something "unusual and dangerous" was being done to them, and reacted with fear and resentment.

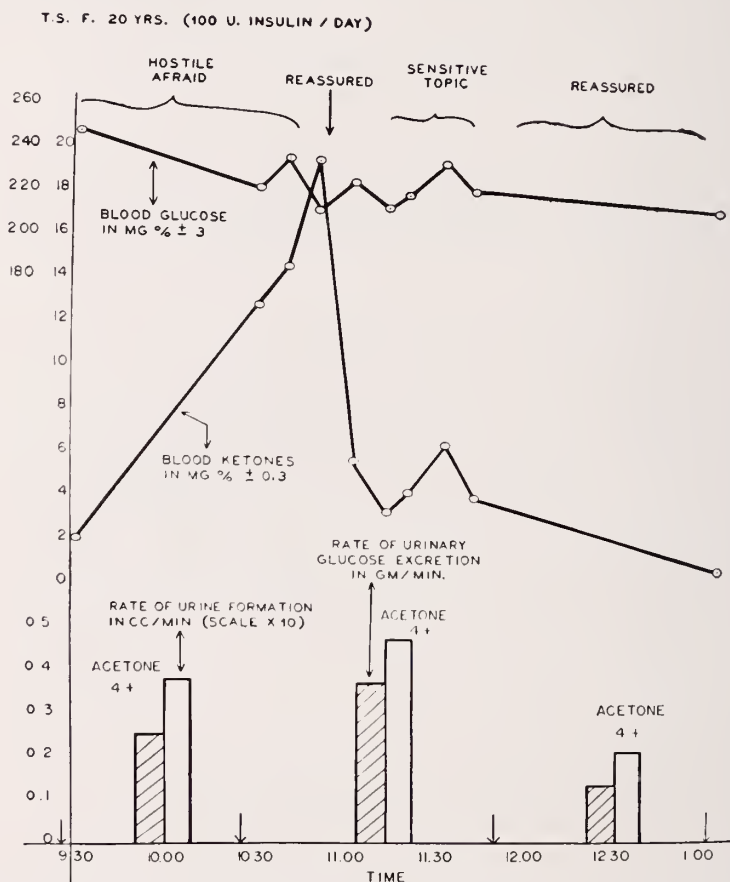


FIG. 10. The effect of a stressful situation upon a diabetic subject whose initial ketone level was 2.0 mg. per cent. A marked rise in the ketone level occurred during stress followed by an equally great fall with reassurance. An increase in urine volume, increased glycosuria, thirst, dry mucous membranes and other evidences of incipient ketosis appeared during the period of stress.

Figure 12 is the protocol of an interview with a 20 year old college student who had many doubts about his manliness, and felt resentful toward his tyrannical father. The initial level of ketone bodies in the hepatic venous blood was less than 0.2 mg. per cent during relative relaxation, but when a discussion of manliness was undertaken a rapid increase to more than 2.0 mg. per cent was observed, and later, following a period of reassurance, sudden rises in ketones were twice induced during a discussion of his conflict with his father.

Later in this paper there is described the case of a diabetic girl in whom a moderately severe episode of keto-acidosis was precipitated by a conflict with her mother. She was under careful observation in the hospital at the time and her diet, insulin, and activity were maintained constant. The keto-acidosis subsided after strong reassurance without additional insulin or other change in

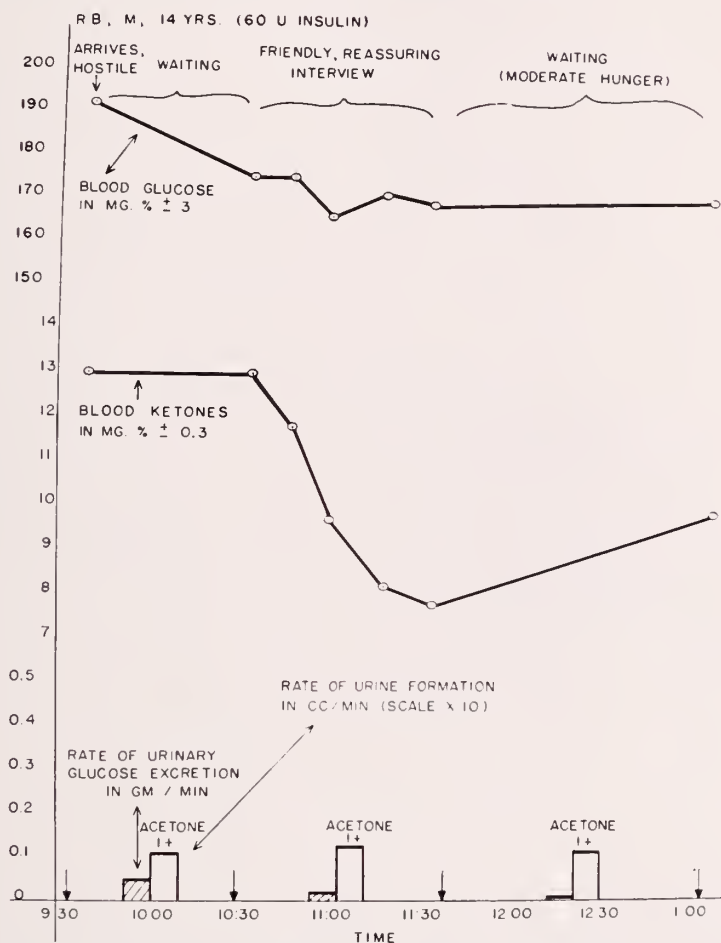


FIG. 11. The amelioration of a relatively high level of ketonemia by the removal of stress through a friendly and reassuring interview.

therapy. We have had the opportunity to observe two similar instances of ketosis occurring under stress in the relatively controlled hospital environment, and others have reported the same phenomenon (36, 37). The experimental observations on this group of diabetic subjects provide further evidence that the ketosis which may occur in association with conflict situations may rapidly lead to a severe acidosis, and even to coma.

The blood ketones during diabetic ketosis and coma usually range between

40 and 200 mg. per cent (38). Since the ketones rose 17 mg. per cent within an hour and a half during the experiment diagrammed in Figure 10, it seems possible that levels in the range of clinical ketosis might have been reached after three and a half hours had the stimulus been maintained. Although the ketone bodies may not in themselves be the cause of coma, a high level of ketonemia with dehydration is a reliable indication of a diabetic decompensation in the direction of coma (39). Such a rapid induction of ketosis might explain such re-

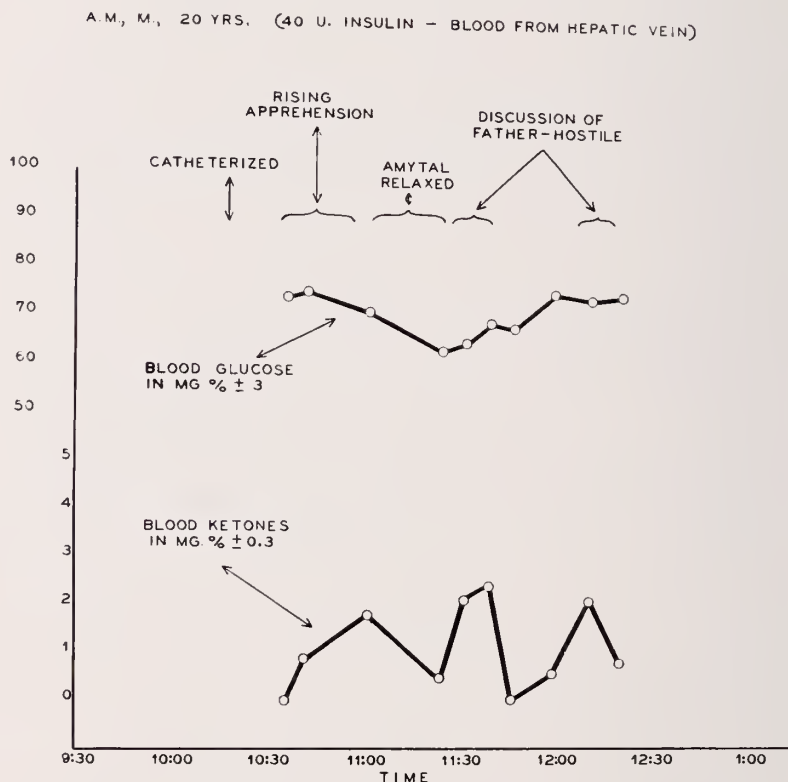


FIG. 12. The effect of an interview upon the level of ketones and glucose in blood samples obtained from the hepatic vein. A rapid rise in the ketones occurred each time a significant conflict was dwelt upon.

ports as that of Von Noorden (40) whose diabetic banker, previously well controlled, attended a stormy meeting of his board of directors, returned home, and shortly became comatose.

It is not practical to assign "normal" values for the blood ketones to a diabetic. Depending upon his previous diet, the length of time since he received insulin, his activity, and, apparently, his life situation, a diabetic may have either no detectable ketones or more than 10 mg. per cent in a fasting specimen on a "normal" morning. Prolonged hypoglycemia is known to lead to ketonemia (41) and a fall in the blood glucose usually precedes a rise in the blood ketones;

but despite these facts, within a wide range of values the blood glucose and ketones are quite independent of each other. In the morning fasting blood of patients without diabetic symptoms at the time, we have observed values of 38.0 mg. per cent of ketones when the blood sugar was 102 mg. per cent, and 1.4 mg. per cent of ketones when the blood sugar was 342 mg. per cent. A patient, without change in diet or insulin, on one morning had a blood sugar of 290 mg. per cent with 0.9 mg. per cent of ketones, and on another morning had a blood sugar of 192 mg. per cent with 13.0 mg. per cent of ketones. Briggs reported similar figures (42). However, it has been our general experience that diabetics who have none of the symptoms caused by either too much or too little insulin, and who are under no stress at the time, have blood ketone levels within the range of those found in the blood of non-diabetics under similar circumstances.

Like the blood glucose, the blood ketone bodies are a source of readily available body fuel. In all tissues except the central nervous system they seem to constitute adequate sources of energy. When the diet is deficient in carbohydrates they appear in the blood in increasing amounts, possibly as a partial substitute for glucose, since aceto-acetate apparently may enter into the tri-carboxylic acid cycle, which is one of the steps through which glucose is converted into energy for muscle contraction (43). Ketonemia may also appear when there is an increased demand for metabolic fuel, as during fever (44) or prolonged and vigorous exercise (45-47). The data from the present experiments indicate that events in the life situation which either directly or through their symbolic meaning threaten the security and well-being of an individual may also call forth an increase in ketonemia. It is as if the perception of a threat led to a metabolic preparation to meet the threat. Such reactions in other bodily systems, such as the cardiovascular system, are well known (48, 49). The evidence from the single experiment with liver catheterization suggests that increased production by the liver is at least in part responsible for this rise in ketones. Since no circumstance has been reported in which the ability of the peripheral tissues to utilize ketones is depressed, it seems reasonable to assume that the entire phenomenon may be caused by an increase in ketone production.* There are two mechanisms known through which stimuli arising in the central nervous system might affect an increase in ketone production. One is the elaboration of adrenalin through the stimulation of the adrenal medulla (50). The other is the elaboration of the hormones of the anterior pituitary and the adrenal as a primary effect of direct stimulation from the central nervous system through pathways as yet unknown. Both the growth hormone and the adrenocorticotrophic hormone of the pituitary stimulate ketogenesis (51), the former by direct action upon the liver, and the latter through its effect upon the adrenal cortex. The fact that during the present studies we have found the circulating eosinophiles to decrease as the blood ketone level rises in response to stressful situations therefore suggests that the adrenal cortex may be involved in the mechanism by which the ketone changes are produced.

* Recent evidence suggests that the capacity to utilize ketone bodies may be enhanced by ACTH and adrenal steroids (61).

FLUID BALANCE

The "normal" human urinary output is about 1400 cc. a day, or 1 cc/minute; but there is a good deal of variation in this "normal" value from day to day, depending upon such changing factors as the amount of fluid consumed by the individual, the physical work he performs, and the temperature of his surroundings. However, if these and similar factors are maintained relatively constant, the post-absorptive, hypopenic man excretes urine at a rate of 0.3 to 1.5 cc/

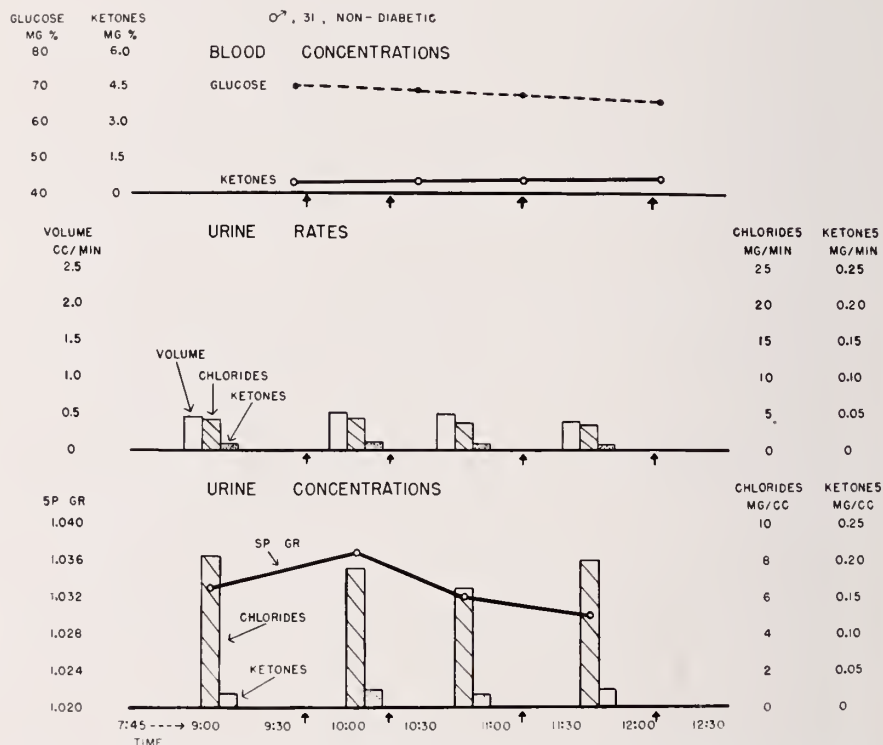


FIG. 13. Diagram of a control study, showing relatively little change in concentration of blood glucose and ketones, in the rate of excretion of water, chlorides, and ketones, and in the concentration of these substances in the urine. Arrows on the diagram represent collection points.

minute, and maintains this rate with constancy over a four hour period. The constituents of this urine—the rate of excretion of chlorides, sodium, potassium, water, and ketone bodies—also change very little during this period of time (fig. 13). However, if the subject is fasted for sixteen or more hours, he often exhibits a transient rise in his urine output, as mentioned earlier (fig. 1). This slight diuresis occurs at about the time that the blood glucose has reached a minimal level and the blood ketones begin to rise, although it is quite independent of these changes in the blood constituents. It appears to be another portion of the adaptive reaction to fasting—the so-called "starvation diuresis." It is characterized

by an increase in water excretion and a somewhat smaller increase in the excretion of electrolytes, resulting in a relative dilution of the urine.

A similar diuresis is readily produced in some normal individuals who are exposed to stressful situations arousing in them feeling states of anxiety or apprehension. Figure 2 is an example of this. A similar phenomenon has been observed in persons exposed to cold (52). It appears that a diuresis of this nature may be a standard bodily response to certain forms of stress.

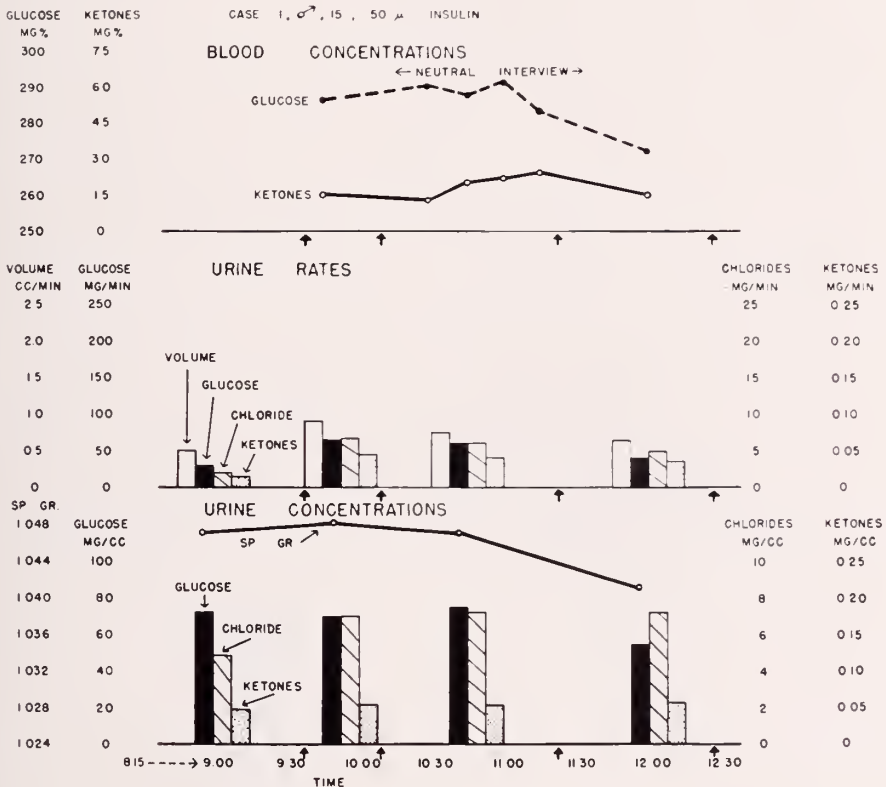


FIG. 14. Diagram of control study showing hyperglycemia and heavy glycosuria not associated with polyuria. Blood glucose 286 mg. per cent, urine glucose concentration 73.4 mg/cc. Normal rate of output of water, chlorides, and ketones.

The diabetic individual likewise excretes urine at a relatively steady rate throughout a four hour period if he is not exposed to special stimuli. During periods when he is well compensated his urine output is in the same range as that of the non-diabetic. Even when diabetic persons have a relatively elevated blood glucose concentration, and large quantities of glucose in their urine, they may have a normal rate of urine excretion at times when they are under no special stress (fig. 14). Under such circumstances the excretion of glucose in their urine is not necessarily accompanied by an excessive loss of water and electrolytes.

A stress diuresis is readily produced in diabetic persons by exposing them to

suitable stimuli. This diuresis is quite independent of glycosuria, and at times occurs even when it is absent (fig. 15). When glycosuria is present and a stress diuresis is induced, the rate of excretion of glucose rises *pari passu* with the rate of water excretion, and the concentration of glucose in the urine does not change even though it may initially have been low. Repeated observations of this sort have led to the interesting conclusion that under some circumstances diuresis leads to increased glycosuria, rather than vice versa, as it has been customary to

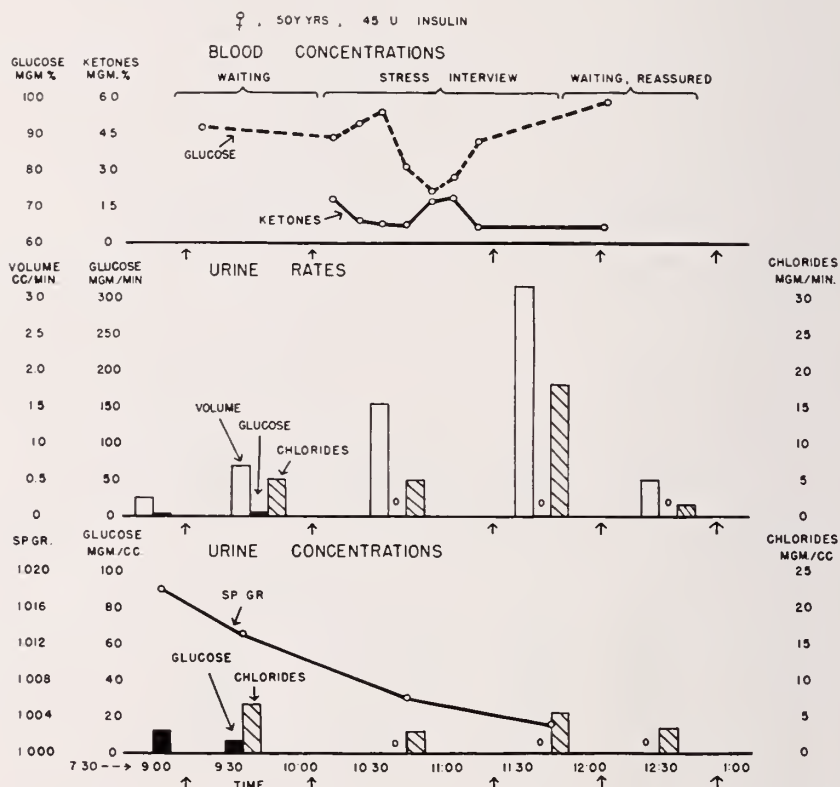


FIG. 15. Stress diuresis occurring in a diabetic subject in the absence of glycosuria. Rate of chloride excretion rises in parallel with rise in rate of water excretion, although specific gravity of urine and concentration of chlorides falls.

assume. It will be recalled from the discussion of the blood glucose above that such a diuresis and increased glycosuria often occur at a time when the blood sugar level is falling (figs. 4, 5, 10). When there is a large concentration of glucose in the urine, induction of a stress diuresis may lead to a prompt increase in the rate of excretion chlorides and fixed base. Under such circumstances chloride losses as high as 25.2 mg. minute (1.5 Gm./hour) have been observed. It has long been known that this loss of electrolytes in association with chlorides is a potent factor in the mechanism of the dehydration which occurs in diabetic acidosis. In addition to this, the ketonemic response to stress is augmented by

the drain on glycogen stores which results when a high level of glycosuria is sustained. Rates of glucose excretion as high as 490 mg./minute (29.4 Gm./hour) have been observed in fasting hydropenic individuals during a stress diuresis. The magnitude of this glucose loss is diagrammed in Figure 16. The two responses to stress—ketonemia and diuresis—appear to be the two physiological mechanisms through which ketoacidosis and coma are induced in humans exposed to stressful situations.

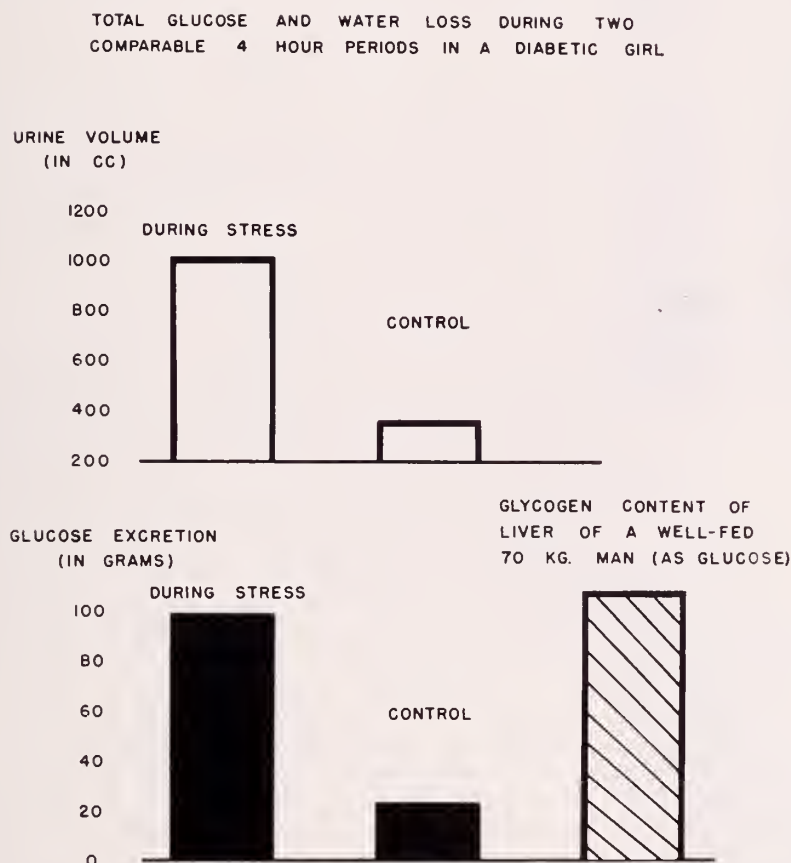


FIG. 16. Magnitude of loss of glucose and water under stress

LONG-TERM STUDIES

The importance of these phenomena in the clinical course of diabetes was repeatedly demonstrated during the long-term studies of the patients. These persons exhibited an unexpected uniformity in many aspects of their life histories (19, 53, 54).

A typical life history of a patient in the series is that of Subject Y, which is illustrated in graphic form in Figures 17 to 20. In the four columns of these charts are diagrammed the temporal correlation between the life situation, the overt

(Y) 17 YEAR SCHOOLGIRL 100 UNITS INSULIN

FATHER
IRISH R.C. LABORER, EASY GOING
CALM, AMBITIONLESS, DOMINATED
BY WIFE

MOTHER
GERMAN PROT. 2ND GEN., STRICT
DOMINEERING, CAPRICIOUS
HARD WORKING, FEARFUL

SIBLINGS
3 SISTERS, 1 BROTHER
7-14 YEARS OLDER
"BABY" OF FAMILY

AGE	SITUATION	REACTION	ATTITUDE & FEELINGS	BODILY CHANGE
0	UNWANTED CHILD REJECTED BY MOTHER			
1	CARED FOR, "SPOILED" BY SISTER		FATHER LOVES, PITIES CONTEMPT (RESENTS FAILURE TO SUPPORT)	
2	OVERPROTECTED ACTIVITY RESTRICTED	REBELLIOUS "FRESH"	MOTHER HOSTILE, RESENTFUL VERY DEPENDENT (INTENSE CRAVING FOR HER LOVE)	CHILDHOOD INFECTIOUS DISEASES
3				
4				
5			FAVORITE SISTER GRATEFUL, LOVES	
6	STARTS SCHOOL FIRST FREEDOM FRIENDSHIPS		HAPPY	
7	SCHOOL TRANSFER LOSES FRIENDS	REBELLS	INTENSELY RESENTFUL TOWARD MOTHER AFRAID OF MEETING NEW SITUATION (DEPRIVED OF LOVE)	NAUSEA, VOMITING ABDOMINAL PAIN [APPENDECTOMY] C DIABETES SUSPECTED

FIG. 17. Diagram of the life history of Subject Y. Part One: Ages 0 to 7 years

(Y) AGE	SITUATION	REACTION	ATTITUDE & FEELINGS	BODILY CHANGE	INSULIN
8	GRADUALLY ADJUSTS TO NEW SCHOOL		HAPPIER		
9	FAMILY MOVES NEW SCHOOL NEW NEIGHBORHOOD NO FRIENDS INCREASED RESTRICTION	REBELLIOUS UNCOOPERATIVE	RESENTFUL AFRAID (DEPRIVED)	POLYURIA POLYPHAGIA RESTLESS "JUMPY"	
10	<u>DIABETES DIAGNOSED</u> MOTHER TERRIFIED FOOD RESTRICTED CONFLICTS OVER INSULIN INJECTIONS	DISOBEDIENT DOES NOT FOLLOW DIET "TRIES TO AVOID INSULIN INJECTIONS"	"I'D RATHER BE DEAD"		
11		OVEREATS "SULLEN"	HOPELESS AFRAID		

FIG. 18. Diagram of the life history of Subject Y. Part Two: Ages 8 to 11 years. The relative severity of the diabetes and the amount of insulin required for control are indicated roughly by the thickness of the two black columns. Arrows represent hospitalizations for ketosis or coma.

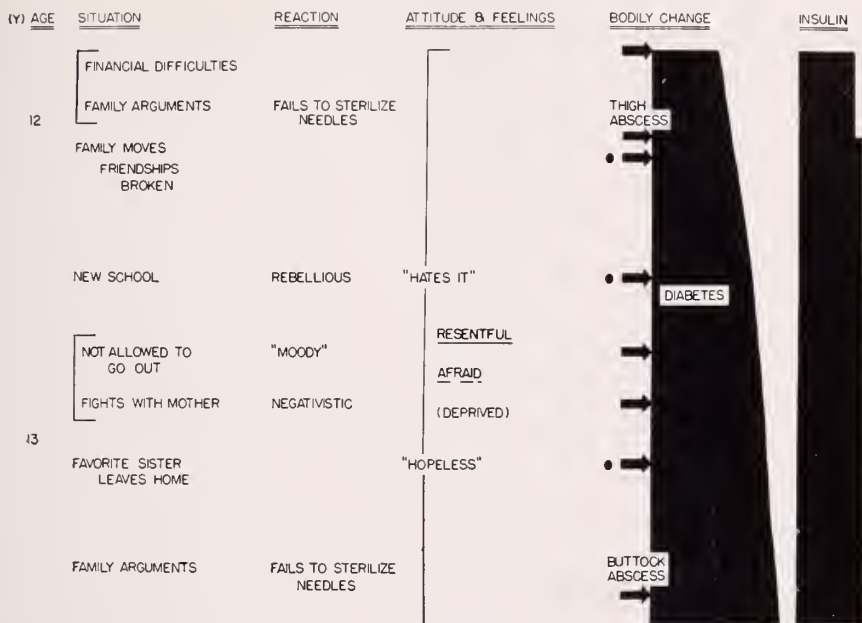


FIG. 19. Diagram of the life history of Subject Y. Part Three: Ages 12 and 13 years. Dots before arrows represent episodes of coma complicated by the cessation of insulin administration after the syndrome had begun.

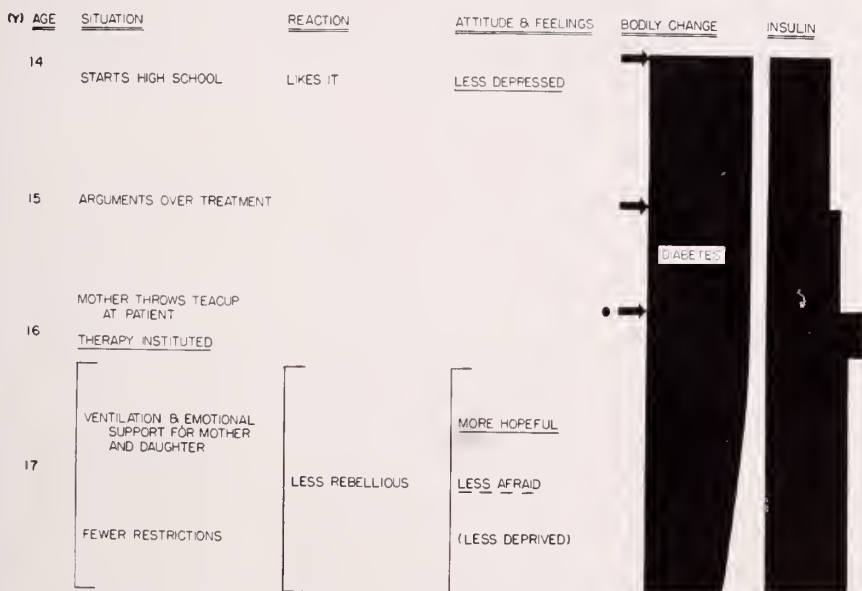


FIG. 20. Diagram of the life history of Subject Y. Part Four: Ages 14 to 17 years

reactions, the attitudes and feelings of the subject at the time, and her bodily reactions which occurred at the same time. Under attitudes and feelings, those words which are underlined are feelings of which the patient was quite aware; those underlined with broken lines were feelings of which the patient was vaguely aware but put into words with reluctance; those in parentheses are those indicated by her dreams, symbolizations, behavior, and associations. The patient was "unaware" of such feelings and attitudes, which in this sense may be said to have been "repressed"; they represent the investigator's inferences from information given by the patient. Attitudes described under "Father" and "Mother" describe the general attitude toward these persons throughout life; it is not intended to imply that such attitudes were present at the age of one year.

This girl was born during the depression, at a time when her father was unemployed and her mother was firing a furnace and acting as janitress in a tenement in order to provide the family with a place to live. The mother was already resentful of her husband for his lack of support, and the addition of this accidental pregnancy late in life added greatly both to her burdens and to her resentment. The child was born at full term, normally, was breast fed, and "a good nurser." The mother rejected the infant from the first, "had no time for it," and turned it over to an elder sister to be reared. She made up for her guilt about this by "worrying about her all the time," demanding strict obedience, and restricting her activity and play severely "so she wouldn't get hurt." She was unable to show any warmth or affection toward the child except by the occasional gift of special food, clothing, or toys. When the child began to demand such special gifts she was considered "spoiled."

The patient's memories go back to this period of restriction in early childhood. She says she "never can remember when mama loved me like I wanted her to." When she started school at the age of five she found herself for the first time in an environment where she had friends and freedom, and felt unconditionally welcome. A year later, when her mother arbitrarily transferred her to a new school she felt acutely deprived. Thereafter she began to eat more and gained weight, becoming a plump child. At the new school, however, she gradually developed friendships with pupils and teachers which supplied for her some of the emotional nourishment which was lacking at home. Nevertheless, she was a shy, anxious, insecure child whose adjustment was tenously maintained. When her family moved again to a new neighborhood and put her in a new school she felt as if she had lost the best part of her life. She was outwardly rebellious, uncooperative, disobedient, and resentful, and inwardly afraid and deprived. Polyuria, polyphagia, and weight loss developed at this time.

When diabetes mellitus was diagnosed the mother was terrified of its implications and more guilty than ever about her feelings toward her daughter. Her reaction to this was greater concern, increased protectiveness and restriction, increased suspicion, and rigid punishment for infractions of the diabetic regimen. The girl felt that she would "rather be dead" and reacted to the diet and insulin as if they were added punishments. She never did follow the diet after the first few weeks of the illness. Her twelve admissions for diabetic acidosis and coma

during the next five years all followed acutely stressful life situations. They are represented by the arrows on the charts. To each of these acute stresses—fights between her parents, arguments with her mother, change to a new school, the departure of her sister (“the only one who loved me”)—she reacted as if it were a threatened deprivation of love and security. They aroused in her resentment, which she felt afraid to express, and were accompanied by the rapid development of thirst, polyuria, ketosis, and coma. On several occasions (marked by dots before the arrow) she expressed her hopelessness and rebellion by stopping her insulin when the ketosis developed. On other occasions she expressed her resentment and hopelessness by failing to sterilize her equipment, and the subsequent infections led to hospital admissions. In half of these instances, however, diabetic coma followed swiftly upon the onset of a stressful life situation, despite the fact that no infection was present, and the insulin dose was not altered. It

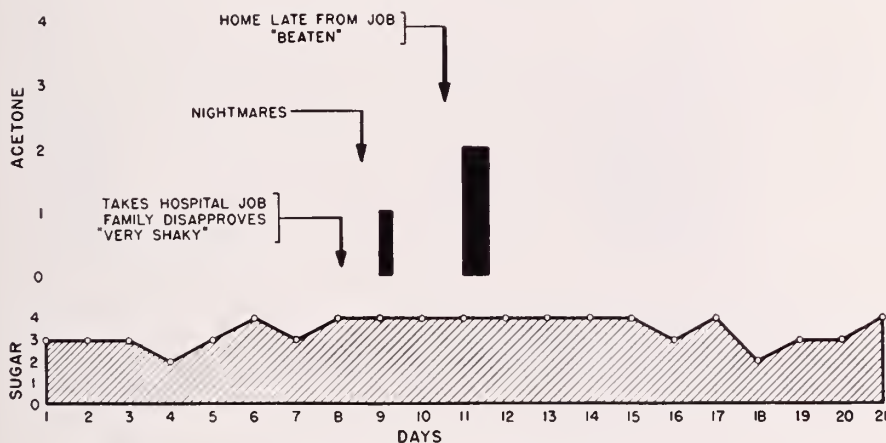


FIG. 21. Chart of daily observations on Subject Y: first three weeks

may be remarked in passing that this patient was typical of the group in that the exacerbations of the diabetic state were in all instances closely related to situational and inter-personal conflicts, and even the “precipitating infections” which appeared at such times were intimately connected with the patient’s life situation.

This girl has now been under observation for four years. During this time the readjustment of her attitudes and behavior and her relations to her mother has prevented her from having any further episodes of ketosis which required hospitalization. When she was first observed she was followed carefully with urine specimens three times a day and fortnightly visits to the clinic. She kept a diary in which she recorded the events of each day and her attitudes and feelings toward them. The occurrences of the preceding two weeks were carefully reviewed at each visit. Her insulin dose was maintained constant throughout. When later the events in her daily life were charted against the results of the urinalyses (figs. 21–24), it was found that there was a one-to-one correspondence between

the occurrence of significant stresses in her daily life and the appearance of ketonuria, thirst, and polyuria. It may be seen from this chart that the day-to-day conflicts to which she had reacted were re-enactments of the situations which

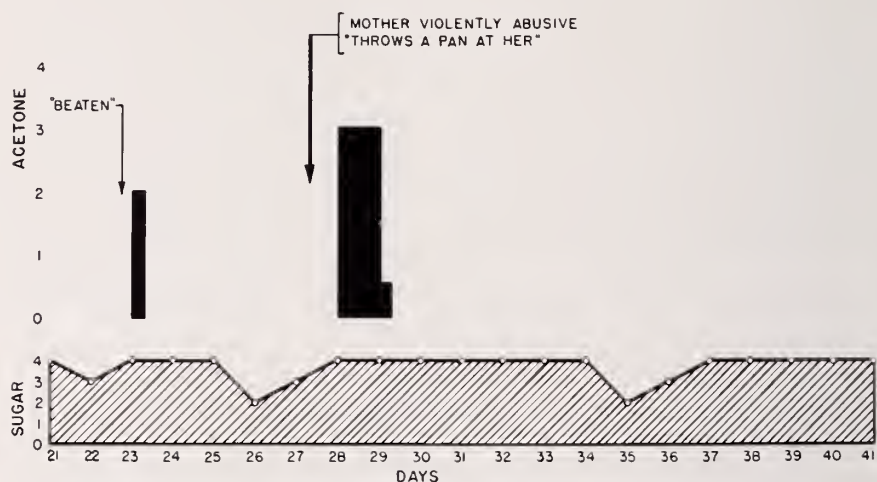


FIG. 22. Chart of daily observations on Subject Y: second three weeks

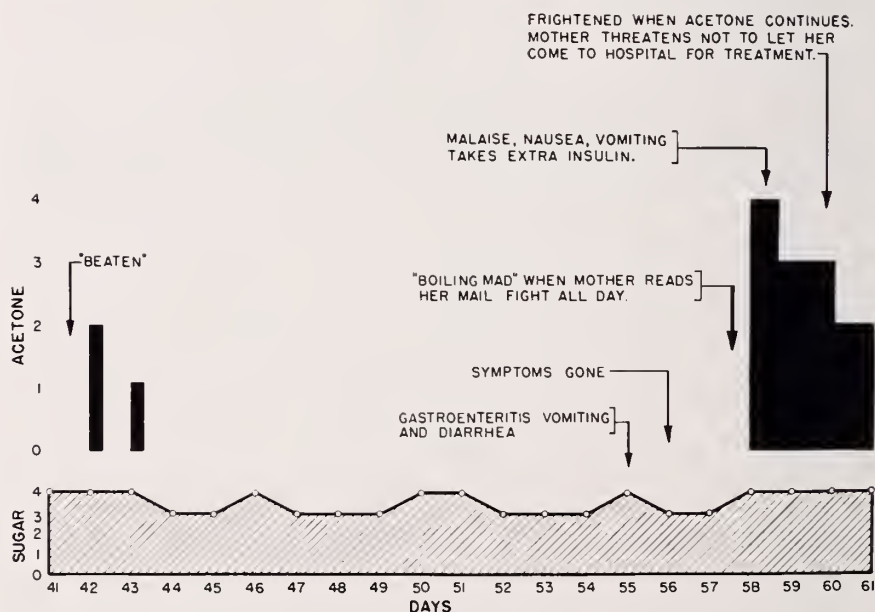


FIG. 23. Chart of daily observations on Subject Y: third three weeks

had been so unsalutary to her throughout her life: attempts to escape from parental restriction and seek outside activities, violent conflicts with her mother, and even a forced change to a new school. When she was admitted to the hospital

on the 71st day and a conflict with her mother was observed under the more carefully controlled conditions of the ward, the dramatic development of a marked ketosis with all of its attendant signs and symptoms left no doubt that the noxious situation itself could produce a full-blown acidosis without the intervention of other factors. She was placed on a regimen of light activity, and a measured intake of 1660 calories, including 200 gms. of CHO, while a mixture of 60 units of protamine zinc insulin and 40 units of regular insulin was administered to her daily. During the course of three days she had no ketonuria and no diabetic symptoms, although she had a moderate glycosuria. On the fourth day her mother visited her. During this visit she gained the impression that her mother was extremely angry with her, and that, furthermore, her physician (her "only friend") was also angry. She became intensely angry, anxious, and

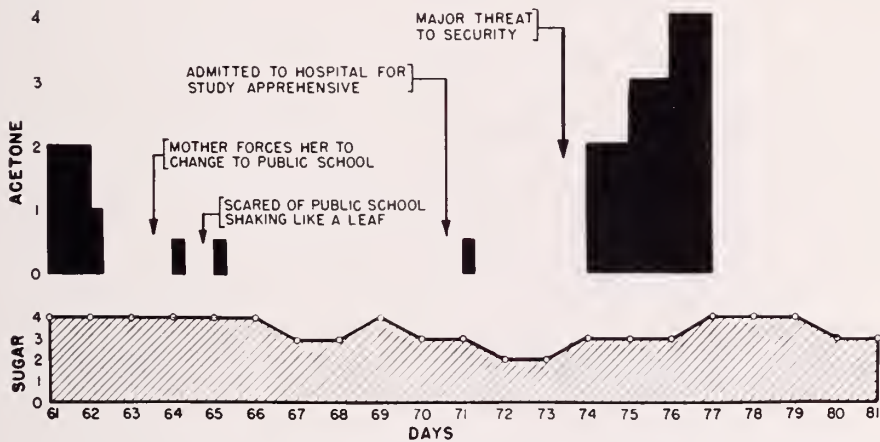


FIG. 24. Chart of daily observations on Subject Y: fourth three weeks. She was admitted to the hospital on the 71st day and remained there until the 81st day; in this setting, under carefully controlled conditions, ketosis was precipitated on the 74th day after an argument with her mother.

depressed, but was unable to express her feelings. During the ensuing night and the following three days she was tense, fearful, sullen and sleepless. Shortly after her mother's visit she complained of thirst, began to drink water copiously, and to urinate frequently. Urine specimens during the night gave a 4-plus nitroprusside test for ketones, and contained large amounts of sugar. When examined the next day she had a tachycardia, dry mouth, dry skin, acetone breath, and some hyperpnea. Thirst, polyuria, and ketonuria continued throughout the day. Despite these alarming manifestations her regimen of diet, insulin, and activity was not changed, but after 24 hours it was explained to her that her mother was not angry with her, and the physician reassured her of his continued friendship and support for her. Without other treatment the ketosis and all of its manifestations disappeared as she regained her calm and security during the next twenty-four hours, and her diabetes remained unchanged during the remainder of her stay in the hospital (55).

The life experiences of this young woman and her reactions to them were remarkably similar to those of the other members of the group. So striking was this observation that one could scarcely escape the inference that life experiences may play an important role in determining the onset of diabetes mellitus, and possibly constitute a factor in its etiology.

THE SPECIFICITY OF THE STIMULUS AND THE REACTION

Although the stimuli which led to ketosis in these diabetic persons have been described as "stressful situations," it was not found that just any sort of a stress situation would produce this type of reaction. Both the situations which led to ketosis and the subject's reaction to them showed a remarkable degree of uniformity. Nearly all were concerned with conflicts with parents or parent figures, or the symbolic representation of such conflicts. Furthermore, careful study of these patients led to the conclusion that each subject reacted to these conflicts as if they were depriving him of the affection and emotional support of the parent figure, and threatening his dependent relationship to this person. This threatened deprivation aroused in each subject an intense and barely suppressed anger, which he was often unable to express because of his fear that such an expression of feeling might do even further damage to his dependent relationship. Ketosis was less likely to occur in situations of conflict when a serious threat to the subject's dependent relationship was not involved or when a relatively uninhibited acting out of the subject's hostility was safe and possible.

Example: A 36 year old housewife with labile diabetes was constantly caught between her conflicts with her alcoholic husband and her domineering and suspicious mother-in-law, who lived with her. She was unable to drive the mother-in-law from the house because she and her husband were dependent upon her for financial support. One day the mother-in-law deliberately smeared paint over a portrait the patient was making, and then sarcastically dared her to complain about it. The patient was intensely angry, but afraid to express her feelings because of her fear of the consequences. During the ensuing night and the next day she passed more than a gallon of urine containing 4 plus sugar and acetone, was constantly thirsty, and voluntarily took 75 units of added insulin, with orange juice and salt broth, in order to control these symptoms.

On a second occasion this woman and her husband went with the mother-in-law on a shopping trip. When the patient returned with the articles she had bought, her mother-in-law sneeringly derided her purchases, and taunted her with the fact that she had wasted the money which she had been given. The patient bore this in silence during the ride home, but suddenly she "just couldn't control myself. I blew up,"—and cracked the old woman soundly over the head with a package of glassware. Much to her surprise the mother-in-law subsided meekly, and the husband supported his wife in her action, blaming his mother for "bringing it on herself." The patient felt not only relieved, but vindicated and triumphant. Although she had been intensely angry, she now felt "happy." She did not develop either ketosis or polyuria.

On still a third occasion her husband and her mother-in-law became involved in a dispute as they were driving the patient to town for what she felt was an extremely important visit to the physician. As the argument became more heated the husband began to drive more and more recklessly. The patient was "afraid to say anything," because if she did she was "afraid she might become involved" and "I might get angry too," which might at worst cause the husband to wreck the automobile, and at least cause him to refuse petulantly to continue the drive. She decided that the only thing to do was to "keep quiet and not let

myself be upset." This tactic worked, but as the drive continued she developed a headache and began to feel "shaky"—symptoms which she usually associated with an insulin reaction. When she arrived at the hospital the urine specimen which she passed contained no glucose, and her blood sugar was 70 mg. per cent, although she had had no insulin for 28 hours and had had a constant glycosuria previous to the time at which this urine was passed.

These three situations, which are superficially so similar, produced three different types of reaction in the patient. The first situation aroused intense hostility toward the parent figure, which the patient was unable to discharge because of fear of the consequences. As these feelings continued ketonuria, polyuria and dehydration developed. The second situation aroused the same feelings as the first, but they were effectively discharged by an impulsive act of aggression. Ketosis did not develop. In the third situation the subject was predominantly anxious but careful to avoid the possibility of a threat to her dependent relationship. This situation was associated with symptoms of hypoglycemia.

THE POSSIBLE BIOLOGIC SIGNIFICANCE OF THESE REACTIONS

H. G. Wolff has suggested (56) that stress diseases and bodily disorders may represent the inappropriate use of adaptive mechanisms which are not only appropriate but effective in dealing with other types of noxious situations. For example, it is easy to see the appropriateness of an explosive watery diarrhea in eliminating ingested meat which is infected with salmonella, and it is also easy to see how this mechanism might be used inappropriately and symbolically to "get rid of" a tyrannical parent. Diabetes mellitus has not been thought of as a similar inappropriate use of an adaptive mechanism primarily because it has not generally been recognized that there could be a life situation to which a diabetic syndrome would represent an appropriate and adequate response. It has seemed, rather, that the disease must represent a defect of some sort.

There is, however, a situation in which the normal, healthy human develops a "diabetes mellitus" which enables him better to withstand the effects of that situation. Such a situation, now less common among civilized peoples, must at one time have been one of the most common of the stressful situations faced by man. It is starvation, or "deprivation of food." In the absence of food for more than about twenty-four hours, the human mechanism ceases in part to metabolize carbohydrate and turns to the use of fat as a body fuel. The respiratory quotient falls, and the liver begins to pour ketone bodies into the blood until they reach levels as high as 60 mg. per cent (57). Furthermore, if carbohydrate is fed to the subject after this syndrome has been established, it rapidly rises in the blood to hyperglycemic levels, producing a "diabetic glucose tolerance curve," and appears promptly in the urine; the serum potassium and inorganic phosphate do not fall, and pyruvic acid does not increase in the blood, as it would if appreciable amounts of glucose were being metabolized by the muscle (58). The "purpose" of this preferential use of fat instead of carbohydrate is apparently the conservation of body stores of glucose. The central nervous system metabolizes only glucose (59), and cannot function effectively in the face of sustained hypoglycemia. The muscles, on the other hand, perform effectively on whole fat or

ketone bodies, as mentioned before. Although the question of the extent to which fatty acids can be converted to glucose is still debated, there is no doubt that a large part of the glucose which is manufactured during starvation is produced from body protein, and that the attendant wasting of body tissues must be kept at a minimum if life is to be prolonged. Many students of the subject feel that protein is the only major source of manufactured glucose. The use of fat instead of glucose is therefore doubly valuable in starvation. Although its function and mechanism have not been thoroughly explored, polyuria has also been a prominent finding in the early phases of starvation (60).

There has been demonstrated no qualitative difference between the metabolism of starvation and that of an early, mild diabetic. Similarly the transitory elevation of arterial pressure of a man under stress utilizes the same physiologic mechanisms as are operative in early "essential" hypertension. When it is pointed out that severe or long-standing diabetes may be associated with coma, arteriosclerosis, nephritis and neuropathy, it may also be pointed out that severe or long-continued hypertension is associated with cerebral thrombosis, arteriosclerosis, nephritis, and cardiac failure; in both cases the long sustained and intense use of an inappropriate adaptive response leads to many secondary, irreversible, and even fatal, consequences. Diabetes mellitus differs from the diabetes of starvation apparently only in that it is an inappropriate response. If a starving man is fed carbohydrate, his metabolism soon responds to the cue that food is present: within a few hours his respiratory quotient rises, his "diabetic tolerance curve" and glycosuria disappear, and the secondary metabolic effects of glucose utilization are seen in the blood. The diabetic does not respond to this cue. The ingested glucose therefore rises in his blood to hyperglycemic levels, and spills into the urine. He seems to continue to use the adaptation to starvation at times when he is not starved.

Why does he do so? An answer has been suggested by the life histories of more than 50 diabetic persons who were studied. It was found that in nearly all of these cases the onset of the disorder occurred after a period of environmental and interpersonal stress characterized by the loss of persons, objects, relationships, or cultural values which the patient had regarded as indispensable to his total security, both psychological and physical. The patients reacted, both consciously and unconsciously, as if they had been deprived of affection and security, for which they showed an intense need; this deprivation aroused in them an intense hostility, which was often focused upon the parent figure whose affection and support they most desired. Their craving for affection was therefore complicated by an inability to accept it.

It is not usually possible, in the adult patient, to get a reliable history of the circumstances surrounding his conception, birth, and earliest development. In some of our patients in whom it was possible to obtain such information it could be seen that even in their earliest infancy and childhood they reacted to such stresses as the illness of the mother, the birth of a younger sibling, or rejection by parents, with an increase in appetite, increase in weight, and demand for sweets; they parents often remarked upon this, saying "He always ate more than the other children" or "He was always asking for sweets, even from the time he

was a little baby." In earliest infancy the relation between food, mother love, and total security is so close that it is doubtful whether any distinction exists from the child's viewpoint. In all individuals the feeling that security and affection are associated with food is strongly conditioned throughout the nursing and early feeding period. The giving of sweets and pastries as rewards and withholding them as punishments is a common way of disciplining children in our culture, and one that seemed to be especially stressed by the parents of this diabetic group. The daily gathering of the family at mealtime, with all that this implies in terms of the scenes and experiences constantly re-enacted there, leads to a prolonged and repetitive conditioning of uncalculated importance in early life. In later life feasts, fasts, parties, and foods of special significance continue to lend to the giving and partaking of food important overtones beyond those of mere satisfaction of hunger. It is not surprising therefore that such concepts as food, security, approval, affection, and friendship should continue to be closely associated in all persons throughout their lives, both on a "conscious" and an "unconscious" level.

Why the diabetic makes this identification more strongly than most persons and continues it more tenaciously is not entirely apparent. The occurrence of diabetes in families and its very early development in some infants suggests that a "constitutional susceptibility" to this type of inappropriate metabolic response may exist. In other patients, however, in whom no family history of diabetes could be elicited, it was apparent that the mothers and fathers had still further conditioned the relation of food and love by handling their child in a cold and rigid manner, without overt display of affection, while at the same time expressing their approval and support only through occasional gifts of special food and other material objects. It may be that this type of reaction can occur either with little or no conditioning in persons with a "constitutional susceptibility," or after strong conditioning and profound stress in persons who have no "constitutional susceptibility."

A theory of the psychobiological meaning of diabetes mellitus may be stated briefly in these terms:

- 1) The metabolic pattern which occurs in diabetes mellitus is an adaptive response to carbohydrate starvation which has developed in the vertebrates in parallel with the increased importance of the central nervous system as the central integrator of the organism. Its effect, when brought into action, is the increase in the use of fat and ketone bodies as the fuel for muscular activity, and the parallel decrease in the use of carbohydrate. The carbohydrate is conserved to minimize protein breakdown and to provide a source of energy for those systems which require its presence, prominent among which is the central nervous system, which is entirely dependent upon carbohydrate and cannot metabolize fat.

- 2) The diabetic pattern of metabolism represents an adequate and effective response of the human to carbohydrate starvation.

- 3) Food, affection, and emotional and physical security are intimately identified in infancy. This "conditioned relationship" is strongly reinforced by childhood training as well as by later adult experiences.

- 4) Some persons, because of constitutional predisposition or strong condition-

ing, or both, in later life respond to cumulative psychological, situational and physical stresses which involve the loss of affection and security, as if they represented threats of starvation. In this situation they utilize a metabolic adaptation to starvation which is inappropriate, and they continue to do so even when food is supplied to them in large amounts. The long continued use of this mechanism is associated with the irreversible changes of structure and function which are associated with diabetes. Acute stresses in the course of diabetes may be associated with ketosis and coma.

SUMMARY AND CONCLUSIONS

1. Experimental evidence indicates that stimuli arising out of the life experience of the individual, which are either consciously or unconsciously interpreted by him as having important relevance to his security, may produce in both diabetic and non-diabetic humans fluctuations in the level of ketone bodies and glucose in the venous blood. The magnitude of these changes is much greater in diabetic persons, and if great enough and of long enough duration they lead to ketosis and hyperglycemia in some cases, and to hypoglycemia in others, without the necessary intervention of other factors such as inter-current illness, changes in physical activity, or alteration of insulin or food intake.

2. Similar stimuli may lead to important changes in the amount of urine excreted by both diabetic and non-diabetic persons. The occurrence of diuresis in a diabetic person under environmental stress may be associated with a massive loss of glucose and electrolytes which is an important factor in the development of dehydration and coma.

3. The life histories of persons with diabetes mellitus, and observations of their responses to events and situations in their daily lives, are consistent with the concept that life experiences are of great importance in the onset and course of the disease.

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PHYSIOLOGICAL CONSIDERATIONS OF EDEMA

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Edema is best defined as a clinically detectable localized or generalized expansion of the extracellular fluid. The underlying difficulty in the recognition of such expansion concerns the method of detection, namely gross clinical observation. At what critical expansion of this fluid compartment does edema appear? This will depend upon factors in addition to volume. It will depend foremost on inherent tissue pressure of the involved area. Loose areolar tissue will accept large volumes before obvious deformity occurs; tight closely bound tissue will conversely resist fluid entrance although it may reveal its secret sooner. Consequently a loose skinned, round infant may expand its interstitial space almost 50 per cent before edema is visible whereas a tightly skinned, cachectic adult will probably evidence the characteristic sign of persistent pitting much sooner. Hydrostatic pressure will on the other hand determine the site at which such expansions become apparent—as the lower extremity in the erect patient, the sacrum in the reclining patient or even the lung in the reclining cardiac. These factors, however, are primarily concerned with the site at which generalized extracellular expansions become visible. What of the approximate volume which must first accumulate before these local factors condition their location? Certainly, it is not infrequent to admit a patient suffering from acute diffuse glomerulonephritis without acceptable evidence of edema and then to observe an 8 to 10 pound diuresis after the institution of proper therapy. Using the inulin space as a measure of the fluid phase of the extracellular compartment we have gradually adduced evidence which indicates that a 3 to 5 liter expansion of the normal extracellular compartment is the usual critical level at which edema may first be manifest. This represents an increment of at least 30 to 50 per cent of the normal space. Certainly, then, under most circumstances in which the degree of edema fairly beckons at the approaching physician, the quantities involved are far greater, presumably 7 to 10 liters.

In order to recognize the presence of 3 to 4 liter expansions of the extracellular compartment, before clinical edema occurs, the physician must constantly be concerned with the state of the organs involved, namely the cells, the kidney and the gastro-intestinal tract. For it is consequent to primary changes in these organs that alterations in the volume of the internal milieu occur. This emphasis on volume change does not preclude careful consideration of the electrolyte composition. It merely reiterates what has long been known: the regulation of composition takes precedence over control of volume—what Gamble called “the medicament position of the body fluids” (2). Significant changes in volume may therefore occur without detectable changes in serum concentration. When alterations in concentration do occur, they are often proportionately smaller

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than the coexistent changes in total volume. In this era of flame photometry, the tendency exists to treat concentrations without considering total volume, often to the detriment of the patient as a whole.

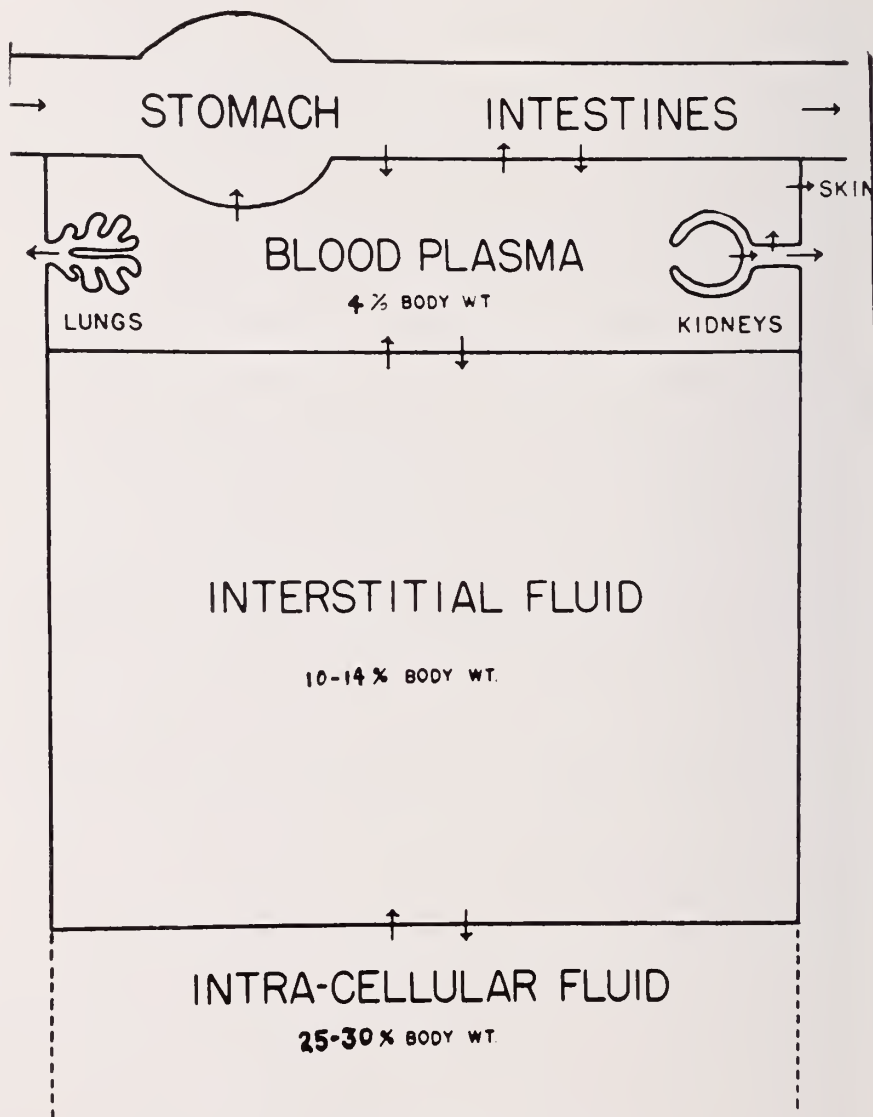


FIG. 1. (as modified from Gamble)

In figure 1, the anatomy of the fluid distributed throughout the body is presented (3). Normally, the plasma volume approximates 3 to 4 per cent of the total body weight, whereas the interstitial compartment equals 10 to 13 per cent. Accordingly the extracellular fluid (vascular plus nonvascular) will approximate 13 to 17 per cent of the body weight, the intracellular compartment 27 to

37 per cent and total water will comprise some 50 to 60 per cent. Chemically, the extra-vascular interstitial fluid may be presumed to represent an ultrafiltrate of plasma, bearing identical sodium, chloride, potassium and bicarbonate concentrations. Whatever small difference in concentration does exist between these two portions of the extracellular fluid derives entirely from the relative impermeability of the capillary wall to protein. This impermeability to a mildly anionic protein complex determines a tiny but constant difference in concentration based on the Gibbs-Doman Equilibrium. For clinical purposes, we may accept that the capillary wall does not offer any resistance to the ready exchange of sodium, chloride, potassium or bicarbonate. This consideration is fundamental because it permits one to calculate the amount of salt retained in a patient with edema by simply estimating that each liter retained contains about 8.5 grams of salt.

In addition, there are relatively solid phases within the extracellular compartment in which the electrolyte composition differs from that of a plasma ultrafiltrate. Specifically, bone contains a considerable excess of sodium and connective tissue (tendon) an excess of chloride (3). These solid phases are not accessible to the molecules which are reputed to offer a measure of the fluid ultra-filtrate phase of the extracellular compartment (inulin, sucrose, etc.). Accordingly, the terms extracellular fluid or compartment, as used in this paper, do not include these areas.

The intracellular compartment is a much more complicated collection of various colloid gels in which the predominant ions are potassium, phosphate and protein, together with smaller but significant amounts of sodium and chloride. The truly remarkable membrane of the body is this cellular membrane which permits two solutions of grossly different chemical composition to lie in immediate proximity and yet to maintain separate chemical identity. Despite the chemical discontinuity at the cell membrane, most investigators presume that osmotic equilibrium obtains between these fundamentally different solutions (4).

The volume relation between these three compartments, namely, plasma, extracellular fluid and intracellular fluid is still under active investigation. The relation between the plasma and the extracellular fluid of which plasma normally represents about one-fourth is defined by Starling's hypothesis. Many doctors seem convinced that the plasma volume, since it represents a portion of the more inclusive extracellular compartment, reflects qualitatively and quantitatively changes in the mother compartment. Actually, there is no reason to believe that such a relation holds true. Figure 2 which represents an extrapolated and idealized version of a variety of data obtained in dog, adult and infant man reveals that wide changes in the extracellular fluid volume may occur with only minimal alteration in the plasma volume, despite fairly constant serum protein concentrations (5, 6, 7). This circumstance is extremely fortunate from a teleological standpoint lest congestive heart failure and shock occur even more frequently. It is only with fairly extreme changes in the extracellular volume that plasma volume begins to rise or fall rapidly. The critical volume of the extra-

cellular compartment concerns that point at which any further increment or decrement will finally destroy the homeostatic barrier of the plasma volume, induce a rapid change therein and a clinical emergency. This critical area in each patient is determined in part by tissue pressure, a variable which cannot be satisfactorily measured.

Those factors which define the equilibrium distribution of fluid between the tissues and the extracellular compartment are poorly understood. Many investigators have presumed that their respective volumes are governed entirely by the osmotic pressure of the electrolytes in the extracellular compartment, specifically the sodium chloride concentration of serum (8). Peters has written that "The chief variable is the sodium concentration of the extracellular compartment,

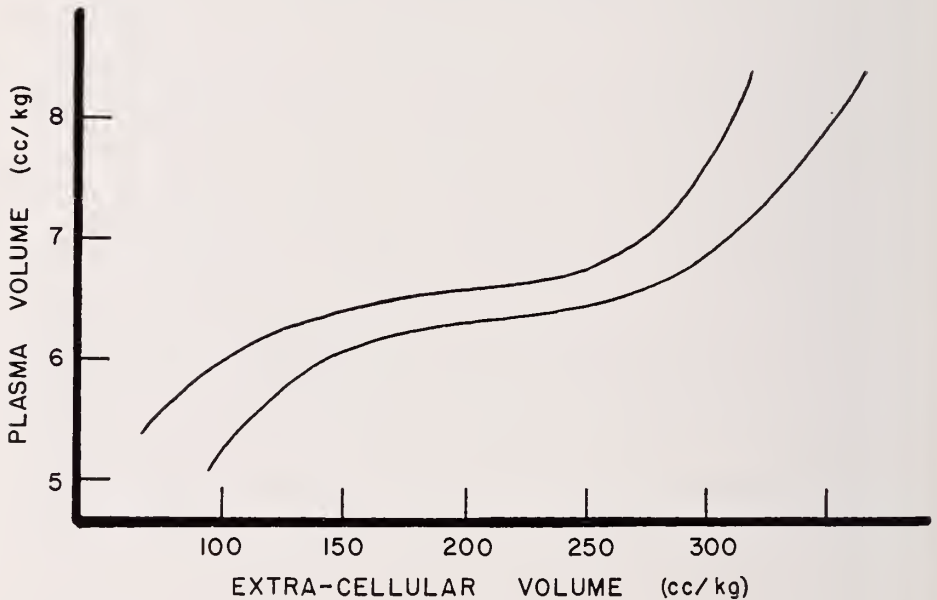


FIG. 2

which is therefore the determinant of the intracellular volume" (4). As this concentration rises, water is withdrawn from cells, as it falls the cells swell. According to this view, the cells are considered as simple inactive osmotic envelopes, the volume of which is fixed entirely by the demands of the extracellular compartment and indirectly by exogenous sodium balance. Although there is no question that cells do react as osmometers, it should also be emphasized that the primary changes may occur within the tissues. In this view the extracellular fluid may not always provide the initial stimulus but may instead reflect the primary changes which have occurred within the active metabolic pool of the cells or of the solid phases of the extracellular compartment. Specifically, it has been demonstrated that adrenal activity causes osmotically active particles (presumably salt) to be extruded into the extracellular compartment with the reverse effect evident during adrenal insufficiency (5, 9). In either view a reciprocal

relation may exist between extracellular and intracellular volumes. Actually, simultaneous measurements made of these compartments in pathological states have confirmed the presence of this inverse relation. Infants convalescing from diarrhea evince expansions of the extracellular compartment almost to the point of edema, while the intracellular volume is depleted (7). On the other hand adrenalectomized animals suffering from severe extracellular dehydration are simultaneously undergoing intracellular swelling (5). This circumstance explains the difficulty in estimating the state of hydration of the sick patient. Clinical considerations of edema or dehydration concern only the state of the extracellular fluid. The cells may be subject to opposite changes.

Classically, alterations in total extracellular volume, as well as in the distribution of this volume between the vascular and non-vascular components, were considered to derive from the mechanics of fluid exchange at the capillary wall. Starling's fundamental hypothesis so beautifully elaborated by Krogh, Landis and Pappenheimer still remains the basic tenet from which all discussions of fluid equilibria must stem (10, 11). Water and its constituents exchange across the capillary wall at rates conditioned by capillary hydrostatic pressure, tissue pressure and the osmotic effect of the non-diffusible protein. At the arterial end of the capillary, where the driving pressure (hydrostatic minus tissue) far exceeds the withstraining osmotic pressure, plasma is filtered out of the capillary bed; at the venous end a progressive fall in driving pressure combined with a gradual rise in osmotic pressure induces a diffusion of fluid in the reverse direction, namely into the capillaries. According to this concept, edema will develop whenever circumstances favor outward filtration or decreased back diffusion—that is, when venous pressure is increased, osmotic pressure decreased, or capillary permeability to protein increased. That this hypothesis governs fluid exchange at the capillary wall and therefore the distribution of water between the interstitial compartment and the plasma, is not questioned. Per se, however, these local changes in capillary circulation can not explain increments in total extracellular volume, except in so far as they initiate a chain of events which specifically expands the volume of the extracellular compartment. More recently many investigators have focused attention on this latter chain of events, not to the exclusion of Starling's hypothesis but rather for its amplification (12, 13, 14).

Whatever the initiating mechanism, it is evident that the presence of edema requires that 4 to 5 liters of water and 35 to 45 grams of salt have been newly deposited in the interstitial compartment. Since most disease states in which edema occurs are not characterized by a marked increase in salt ingestion, such a progressive accumulation can obtain only after a prolonged period of decreased salt excretion. As an example, let us presume that a nephrotic has gained 30 pounds in weight before seeking medical advice. To retain 13 to 15 kilos of water, he must likewise have retained approximately 120 grams of salt. Normally, he probably ingests about 6 to 10 grams of salt per day. Provided that his urine becomes virtually salt-free, which is indeed possible, such an expansion cannot occur in less than two weeks. Chronic overexpansion of the extracellular

compartment can therefore ensue only after prolonged renal retention of salt. In those situations where edema may accumulate very rapidly, as after a myocardial infarction, or during cortisone therapy or post-operatively (in the absence of massive saline infusions), mechanisms other than renal must be involved. Some evidence has been recently accumulated which suggests that, under such circumstances, the tissues may pour significant quantities of salt into the extracellular fluid. (5, 6, 7). Whether related or not, we are limited thereby to two specific techniques for extracellular augmentation; first, a gradual process dependent on salt retention and second, possibly an acute mechanism dependent upon endogenous redistribution of salt in the body.

The frequency with which the kidneys retain salt is reflected in normal renal function. Usually 17 to 18 meqs of sodium are filtered by the adult glomeruli per minute. The renal tubule avidly withdraws 90 to 95 per cent of this filtered load, leaving only about 5 per cent for excretion. About 70 to 80 per cent is actively absorbed in the proximal tubule, and the remaining 10 to 15 per cent in the distal tubule. So eager is this reabsorptive mechanism, that the addition of a strong osmotic load to the tubular fluid will inhibit only a small proportion of this active reabsorption (15). The most obvious facility by which the kidney may retain salt is by increasing the proportion of load reabsorbed. Virtually 99 to 100 per cent of total filtered sodium may be absorbed under such circumstances. Many investigators have tried fruitlessly to assess quantitatively this increment of salt absorption. An increase of 3 per cent in reabsorbate (from 95 to 98 per cent) could easily induce a daily expansion of extracellular volume of 500 to 600 cc. With methods accurate to 5 to 10 per cent, such minute increments are simply not detectable (16). Whatever the active mechanism responsible for this capacity for salt reabsorption, the tubule seems to have been perfectly devised as a salt retaining organ.

The adrenal gland appears capable of directly influencing the distal tubule, thus further stimulating complete absorption of salt. Hyperactivity of the desoxy-like hormones of the adrenal have therefore been implicated in the etiology of clinical edema. It seems pertinent, however, to emphasize that the trend to implicate adrenal overactivity in the causation of clinical edema may be fallacious. Although these hormones do evoke an acute reduction in salt excretion in normal man or in the dog, if their administration is prolonged, the salt retaining influence gradually fades and is replaced by an opposite effect, one of salt diuresis. If DCA is administered to a dog for 2 to 3 weeks, the original expansive stage of the extracellular volume reaches its peak after 10 to 12 days, a salt diuresis called "diabetes insipidus like" ensues and the extracellular volume reverts toward normal despite the continued injection of the hormone (5, 17). The natriuretic effect of DCA in patients with Cushing's syndrome provides the basis of a diagnostic procedure (18).

Prolonged cortisone or ACTH therapy likewise induces such a curve of reactions, salt retentive at first, then natriuretic (19). This latter phase may underlie the therapeutic value of these agents in the treatment of the nephrotic syndrome. Only in the adrenalectomized animal or the Addisonian does prolonged adminis-

tration of DCA continue to exert its typical effect (extracellular augmentative) (5). This suggests that if the adrenal is involved in the production of chronic edema, some state of partial hypoadrenalism may also prevail.

Other hormones including estrogens, androgens, growth hormone and pitressin have been implicated in the development of edema (the latter particularly in hyponatric states associated with edema), but their precise influence remains unknown. Certainly the prolonged effects of these hormones must be evaluated, possibly in contrast to their acute effects, before their proper place in the role of edema formation can be gauged.

Another less well recognized but equally relevant salt retaining factor in man concerns the relative stability of the human glomerular filtration rate. In other species, notably the dog, sudden increments in salt intake and consequently extracellular volume will evoke a prompt increase in glomerular filtration rate and a copious salt diuresis. Man is burdened with a glomerulus that does not so readily accede to changes in salt intake. Expressed in terms of salt per kilogram, the dog is thus capable of rapidly excreting six to eight times the quantity of salt which will produce edema in man (20). Alternatively, an actual reduction in glomerular filtration rate, which characterizes several important disease states such as congestive heart failure, glomerulonephritis, marked depletion of circulating blood volume, will per se enhance the complete absorption of filtered salt. Although this diminution in filtration rate may not be the primary locus by which salt retention occurs, there is now little doubt that it will serve as an additional technique for extracting tubular salt (13).

The human kidney *via* its stable glomerular filtration rate and its facility for reabsorption of the vast bulk of proffered salt load is almost constantly on the verge of salt retention. Of practical concern, are the specific trigger mechanisms which activate these latent salt retaining facilities. One factor which has been recognized as an initiating stimulus is a decreased plasma volume—a plasma volume decreased consequent to direct blood loss or to changes in capillary exchange in accordance with Starling's hypothesis (4). There is no doubt that marked reductions in plasma volume provoke salt retention both via increased reabsorption and reduced filtration. Dr. Homer Smith once wrote, however, "The kidney cannot be concerned with the volume of the plasma as a whole provided no change in concentration of water and electrolyte presented to it has occurred" (21). Possibly this statement will have to be revised but the fact remains that small or moderate changes in plasma volume without coexistent changes in concentration or reductions in filtration rate have not been demonstrated to produce a direct and consistent effect on the renal handling of salt. As inviting as this concept would be, it seems more prudent to reserve judgment on the influence of small decrements or increments in plasma volume on salt excretion until convincing data are forthcoming; until it is proved or disproved that receptors sensitive to changes in plasma volume predictably influence renal function. Regarding the volume of the extracellular compartment as a stimulus for salt retention, here, too, similar confusion exists. There are some data available in dog to indicate that at least in this species, the glomerular filtration rate

is conditioned qualitatively and quantitatively by alterations in extracellular volume (5, 20, 22). Although this relation may be spurious and stem from two independent simultaneous effects, rather than from a true cause and effect system, it has served efficiently to protect this species from edema. In man, however, there is even less reason to hypothesize such a relation between extracellular volume and glomerular filtration rate (23), as evidenced by the greater frequency of edema and by the presence of reduced glomerular filtration despite markedly expanded extracellular compartments. Nevertheless, it has been known since the classical work of McCance on human dehydration that marked reductions in extracellular volume will effect a sharp reduction in the renal excretion of salt (24). Some observers have been so impressed with this dehydration reaction, that all salt retaining states have been attributed to reduction in plasma volume or extracellular volume. Peters, rejecting the use of T-1824 as an index of plasma volume, has concluded that congestive heart failure represents a typical renal response to persistent reductions in plasma volume consequent to increased venous pressure (4, 25). Whatever its ultimate resolution, the problem of the renal response to changes in plasma and/or total extracellular volume poses a crucial and as yet incompletely understood facet of fluid research.

Borst has emphasized the hypothesis that salt retention may result from any decrease in cardiac output; almost as if an expanded extracellular volume would by virtue of its influence on plasma volume provide greater venous return and thereby augmented stroke volume (26). Certainly Selkurt's and Blake's observations demonstrating that a reduction in renal arterial pressure will produce a salt retaining effect, are in accord with Borst's hypothesis (27).

Very recently, it has been noted that changes in local venous pressure influence salt excretion. Harrison and his group report increased salt and water excretion following compression of the neck veins. This effect they attribute to the presence of volume receptors in the brain, which, concerned with the congestion, direct the kidneys to excrete more salt (28). Blake and his colleagues observed reduced homolateral salt excretion after interference with venous flow from a single kidney (29). Others have reduced salt excretion by obstructing venous return in the inferior cava above the kidney, below the kidney and even in the femoral veins (30, 34). These observations juxtapose well with Borst's contention and provide another wide group of stimuli for the conservation of salt. In this day of adrenal consciousness, stress reactions of all type may precipitate salt retention by increasing adrenal activity.

Many of these mechanisms provide plausible explanation for salt retention in some clinical states; none has universal applicability. Even more distressing is the circumstance that most of these stimuli have been studied only as precipitating agents for acute changes. Some experimental results have been obtained only in the dog which notoriously handles salt differently from man. It requires a long hop, skip and even a prayer to extrapolate from data obtained in an acute experiment in which salt excretion is reduced for a matter of minutes or even hours to a satisfactory explanation of prolonged, perpetuated retention of salt, the most important prerequisite for the development of clinical edema.

The alternate general facility for extracellular augmentation, endogenous redistribution of salt and water, will probably undergo considerable clarification in the next decade. Until ten years ago, most physiologists considered the cell membrane as an inviolate barrier which maintained cellular and extracellular electrolytes as distinct, separate and unexchangeable entities. Water was considered to pass across the cell membrane according to osmotic dictates but potas-

Salt retaining syndrome

(Situations in which renal excretion of salt is decreased)

<i>Syndrome</i>	<i>Mechanism</i>
1. Congestive heart failure	
2. Nephrotic syndrome	
3. Cirrhosis	
4. Diarrhea	Decreased extracellular and plasma volume with secondary reduction in glomerular filtration rate?
5. Dehydration	
6. Pyloric obstruction and alkalosis	
7. Salt free diet	
8. Acute glomerulonephritis	Decreased glomerular filtration rate
9. Anuria	
10. Chronic renal disease	
11. Premenstrual edema	Adrenal or gonadal hyperfunction?
12. Early pregnancy	
13. Cushing's syndrome?	
14. Addisonian treated with DCA	
15. Cortisone, ACTH and DCA therapy	
16. Shock	Decreased cardiac output with secondary influence on renal function? decreased plasma volume?
17. Myocardial infarction	
18. Bleeding peptic ulcer	
19. Serum sickness	Increased capillary permeability with decreased plasma volume?
20. Angioneurotic edema	
21. Phlebitis	
22. Acute glomerulonephritis	
23. Hypoproteinemia	Decreased plasma volume?
24. Following surgery or even anesthesia	Unknown
25. Lobar pneumonia	
26. Hepatitis	
27. Poliomyelitis?	
28. Infectious diseases?	
29. Anemia	
30. Hypothyroidism	
31. Specific toxemia of pregnancy	

FIG. 3

sium was locked within the cell and sodium and chloride excluded therefrom (31). More recently this concept has been thoroughly refuted. By means of newer radioactive techniques, it has been demonstrated that cellular potassium is in rapid exchange with the extracellular compartment and furthermore that there exist significant stores of intracellular sodium and chloride in equilibrium with the extracellular compartment (32). Several patho-physiological conditions which are known to provoke salt retention also effect a shift of salt and water into the interstitial fluid. The sodium and chloride contained in the solid phase of bone

and connective tissue, respectively, may provide some of this salt. Up to this point, however, this redistribution has been induced only as a short-lived, acute phenomenon during cortisone or DCA therapy, after plasma volume depletion, systemic dehydration, and general anesthesia (5, 6, 7, 34, 35). Whether the methods employed (inulin space) to detect these shifts will survive the acid test of continued critical evaluation remains to be determined (36). At present, however, these observations suggest tentatively that those stimuli which induce salt retention may also evoke acute redistributions. The varied clinical situations in which edema or other signs of extracellular expansion occur before renal retention of salt could provide adequate explanation, likewise imply that salt retention and salt redistribution may be interrelated processes. In this view, the redistribution provides an acute expansion of the interstitial compartment until the renal mechanism induces a more gradual augmentation of volume. In the opposite direction, the movement of sodium back into the tissues noted to occur after 7 to 9 days of ACTH therapy coincides with the usual onset of sodium diuresis (6).

Figure 3 lists the wide variety of specific syndromes which are characterized by renal retention of salt and expanded extracellular volumes. In many of these states, the initiating mechanism is fairly well understood; in others, as in the last group, no distinct physiological basis has been established. Many of these syndromes are not usually considered to be edema provokers, merely because whatever trigger mechanism initiates the salt retention does not perpetuate it, or simply, the salt retention is an acute affair.

These remarks are not intended to charge the kidney with primary responsibility for the symptoms of congestive heart failure, cirrhosis, or even run of the mill phlebitis. Instead they are designed to denote that long standing expansion of the extracellular compartment cannot obtain without prolonged retention of salt by the renal tubules. Not that these tubules represent the culprit but rather "the victim"—a victim which resorts to basic inherent traits whenever its security is threatened—and that fundamental reaction to a multitude of threats is salt retention.

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SOME THEORETICAL AND PRACTICAL ASPECTS OF THE USE OF FOLIC ACID ANTAGONISTS IN HUMAN NEOPLASIA

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During the past decade the search for a "rational approach" to the chemotherapy of cancer has been greatly accelerated by the demonstration that a variety of chemical agents manifest tumor-inhibiting properties in experimental animal neoplasms. Nevertheless, the agents appropriate for clinical use today, with the possible exception of the steroid hormones, exhibit a narrow dose range within which clinical palliation may be obtained, as well as a characteristic injury to certain normal tissues of the patient. The folic acid antagonists, recently developed as a result of the work of SubbRow (1), Lewisohn (2), Farber (3) and their various collaborators, likewise present the clinician with difficult problems in dosage, techniques of administration, toxicity, and clinical evaluation.

Toxicity: Both the tumor inhibitory effect and the toxicity induced by "folic acid antagonists" in experimental animals are preventable (4, 5, 6, 7, 8, 9) concomitantly by the proper administration of citrovorum factor or, under specific conditions, its precursor, folic acid. When the limited number of clinical observations (10, 11, 12, 13) are interpreted together with studies of the mechanism of action in animals (5, 12, 14) it is apparent that a folic acid-citrovorum factor deficiency state, usually associated with one or more clinical signs of toxicity, is the *sine qua non* in any therapeutic evaluation of these metabolic antagonists in human neoplasia. This deficiency state cannot be induced with complete safety or precision in man. As yet, convenient methods have not been adopted for measuring (15, 16) the absorption, blood level, and excretion of either of the metabolites; and there is only fragmentary data (14, 16, 17) concerning the fate of the folic acid antagonists in the body.

The central problem in the clinical evaluation of the folic acid antagonists consists of the induction of a deficiency state with a minimum of risk to the patient. It is obvious that, as in the case of most of the tumor-inhibiting substances, including such clinically-useful agents as nitrogen mustard, triethylene-melamine and urethane, homeopathic dosage will be particularly unrewarding.

A detailed study of the toxicity of the folic antagonists in lower mammals has contributed many data which should be of value to the clinician. In small rodents, as in man, the toxic (deficiency) state is characterized by certain well-defined features which provide a crude guide for clinical studies. These features, based primarily on studies with aminopterin, may be summarized as follows:

1. The toxicity of the antagonist is qualitatively similar and occurs at the same

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- dose level, whether oral or parenteral routes of administration are employed (5) *i.e.*, absorption appears to be complete.
2. The absorption and fixation of the antagonists at physiological loci (5, 14) occur promptly—in a matter of minutes (fig. 1).
 3. The toxic state is characteristically delayed and develops slowly—usually first becoming manifest three to five days (fig. 2) after any dose or series of doses (6, 14).
 4. Essentially complete regeneration of the enzymes affected by the antagonist occurs in from five to seven days (fig. 2) after any single dose or series of doses (6, 14).
 5. If endogenous or exogenous sources of the metabolite remain constant and the rate of regeneration of the enzymes keep pace with the rate of destruction, it may be assumed that the toxic state will fail to develop (14).
 6. The dosage regimen cannot be based on the size of the individual single or daily dose, since the maximum single dose which can be tolerated when given repeatedly at five to seven day intervals far exceeds (5, 6, 14, 19) the total dose which can be tolerated when fractionated daily. Dosage in man appears to be best calculated on the basis of time-dose-response (14) factors (*v.i.*) covering periods of approximately one week.
 7. Folic acid will fail to prevent the toxicity of the so-called folic acid antagonists except under limited conditions of timing and dosage (5). In contrast, citrovorum factor, a formyl derivative of folic acid (20) is capable of preventing (6, 7, 10, 14, 17) but not truly reversing the toxicity of the antagonists over a wide range of temporal and stoichiometric conditions.

Mechanism of action: The conversion of folic acid to citrovorum factor is mediated by an enzyme (21, 22) designated (14) as enzyme A (figs. 1 & 2). This enzyme is inhibited completely in a prompt irreversible (fig. 1) and non-competitive manner by a single dose of antagonist (aminopterin) so small (14) as to be devoid of obvious physiological effects. This acute deficiency or inactivation of enzyme A leads to no apparent ill effects (5, 14) as long as sufficient endogenous citrovorum factor remains available to permit survival of the host during the five to seven day period necessary to regenerate or release enzyme A. This has led some investigators (23) to comment that enzyme A may not be essential for mammalian life and that folic acid is a non-essential vitamin.¹ In contrast, citrovorum factor acts as an essential substrate (21, 22) for a vital enzyme, designated (14) as enzyme B, and is presumably used to produce an unknown substance, herein designated as X, essential for the formation of nucleoprotein. Competition between citrovorum factor and the antagonist, aminopterin, for enzyme B is competitive within certain limits, *i.e.*, the binding of the enzyme is partially reversible (fig. 1), for a few hours after a dose of antagonist has been administered. Much larger doses of antagonist are required to block enzyme B than are required to block enzyme A (figs. 1 & 2). Thus, it may be presumed that the predominant effect of the first few doses of the an-

¹ Under normal nutritional conditions, folic acid must be considered to be the necessary precursor in an essential metabolic process.

tagonist, as employed clinically, is to inhibit progressive increments of enzyme A. When such doses at a potentially effective level are continued, successive increments of enzyme B are also inhibited until essentially complete binding of the enzymes (fig. 2) occurs. Toxicity and even death would be expected three to five days after the dose which induced a complete inhibition of enzyme B. Exogenous citrovorum factor has been shown to compete successfully only with further doses of the antagonist for any remaining *functioning* increments of enzyme B. Thus, it prevents the progressive induction of toxicity and permits survival of the host until re-establishment of the normal enzymatic conversion of folic acid. The effect of citrovorum factor on toxicity is not actually one of "reversal"; for an impending lethal state, once fully established by complete inhibition of enzyme B, cannot be reversed regardless of the amount of metabolite administered.

Since both enzymes A and B recover more or less simultaneously in five to seven days (14) after a toxic non-lethal dose, the speed of recovery from an

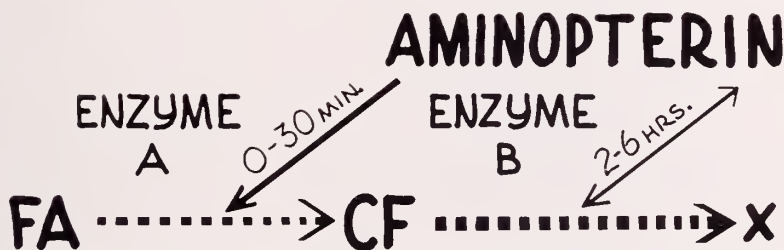


FIG. 1. Diagrammatic representation of the action of a single dose of aminopterin on enzymes presumed to be involved in the utilization of folic acid (FA) and citrovorum factor (CF). Although enzymes A and B have not been isolated from the mammalian liver or fully characterized, there is much indirect evidence from liver-slice and in vivo studies to suggest that the antagonist exerts a prompt non-competitive inhibitory effect on enzyme A. Enzyme B is represented as the site of a competition between metabolite (CF) and antagonist. (See text for further details.)

established toxic state cannot be markedly hastened by the administration of citrovorum factor. The normal conversion of folic acid to citrovorum factor is usually re-established at a time when the host resumes a normal nutritional intake of folic acid.

THE DOSAGE REGIMEN

Among the numerous folic acid-citrovorum factor antagonists thus far investigated² there have been no significant differences (24) in either therapeutic ratio or mechanism of action. For this reason it would appear preferable to employ either of the two most-thoroughly investigated of the available potent

² Aminopterin (4-Aminopteroyl glutamic acid), Amethopterin (4-amino-9-methyl pteroyl glutamic acid), A-ninopterin (4-amino-9-methyl pteroyl glutamic acid), A-denopterin (4-amino pteroyl aspartic acid) and aminopteropterin are included among the series of antagonists, which are analogues of folic acid. Teropterin (pteroyltriglutamic acid) and Diopterin (pteroyldiglutamic acid) are metabolites which substitute for folic acid and manifest no tumor-inhibitory action.

compounds, *i.e.*, aminopterin or A-methopterin. Ten milligrams of amethopterin approximates (12) one milligram of aminopterin in potency in man. The tolerance among adults with diverse types of metastatic carcinoma usually varies from one to two milligrams of aminopterin, or 10 to 20 milligrams of amethopterin, administered daily for many weeks; patients with acute leukemia or rapidly disseminating lymphomas tolerate approximately half of these doses. A reduced tolerance may also be expected in the presence of starvation, severe infections, uremia (myeloma) and possibly during the administration of testosterone (12).

The clinical signs of toxicity do not usually develop prior to the fourth to seventh day after commencing treatment, even with daily dosage at the upper limits of the toxic level. In many instances, slightly lower dose levels (10–20%) will fail to evoke signs of toxicity until the second week of treatment. For these

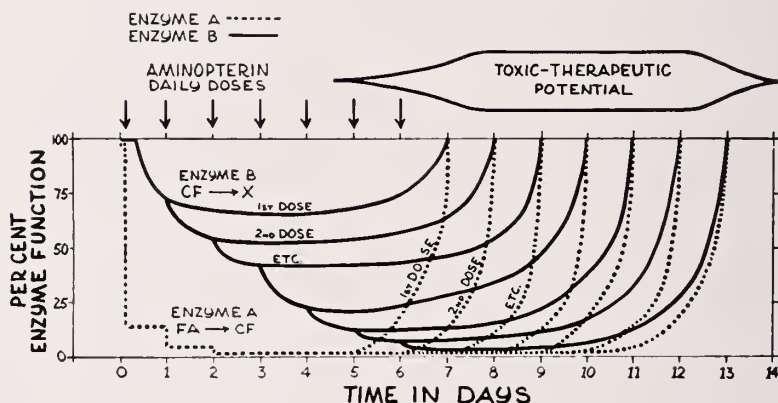


FIG. 2. Diagrammatic representation of the presumptive action of a clinically-effective daily dosage regimen of aminopterin. The function of enzymes A and B is represented on the ordinate. It may be noted that the effects of the antagonists are characteristically delayed and under usual circumstances would not be expected to develop until the second week of treatment at an effective (toxic) dosage. (See text for detailed explanation.)

reasons, treatment for less than one week is usually inadequate. For maximum safety, the daily dose of antagonist should be increased stepwise at intervals of not less than five to seven days. The sequence of toxic signs during development of the deficiency state usually differs among patients with acute leukemia and lymphomas when contrasted to patients with carcinomas. In the former, signs of bone marrow hypoplasia usually precede (12) the onset of upper gastrointestinal ulceration, whereas in the latter the reverse is usually observed. Because of the frequent occurrence of a pre-existing pancytopenia and the absence of oral ulceration during the toxic phase in patients with acute leukemia, bone marrow examination during the five to twenty day period after treatment has been instituted should be relied upon to aid in the adjustment of the dosage schedule. It has been noted (12) that buccal ulceration, which failed to appear during the toxic state in the first course of therapy, subsequently appeared when the toxic state was induced with higher dose levels during a partial or a com-

plete remission. When the toxic state was repeatedly induced over a period of one to two years after initial remission in patients with acute leukemia, the increase in the daily dosage required to produce toxicity never exceeded 75% to 100% (12, 24) of the initial dosage regimen employed.

RESULTS

Acute Leukemia: A rigidly controlled study of survival statistics in children with acute leukemia treated with or without these anti-metabolites is not available. Most patients in the larger treatment centers have received "total care" (24) including antibiotics, transfusions and hormones. Prior to the introduction of the folic acid antagonists in 1947, the "spontaneous" remission rate varied from four to ten per cent (24, 25). These remissions rarely exceeded three months in duration. There is now good evidence that from three to eight months of useful life are provided most patients by a treatment regimen in which the folic acid antagonists appear to play an important role.

From fifty to ninety per cent (24, 26) of children with acute leukemia may be expected to respond favorably during an initial adequate course (one to two weeks) of treatment. Such responses have usually occurred in the acute lymphoid type ("stem cell"; "one-cell type" marrow) of leukemia rather than in the type clearly distinguishable as myeloblastic. Rapid shrinkage of infiltrated organs, together with marked improvement or a return to normal in the hematological findings characterize these remissions. A small number of patients (10-20%) will demonstrate several favorable responses over a period of a year or longer.

The clear cut development of tumor resistance has been observed in some instances after prolonged maintenance therapy or repeated intermittent courses during which toxic signs and favorable responses had been repeatedly induced. A syndrome resembling Banti's Syndrome with signs of hepatic insufficiency and fatal uncontrolled bleeding may occasionally develop during prolonged therapy. At autopsy, there may be little or no pathological evidence of leukemia in such cases. Portal cirrhosis of the liver was observed in at least two instances (12, 26). The influence of repeated absorption of infiltrated neoplastic tissue and shrinkage of the liver appear to be involved in this interesting finding. It should be noted that the anti-metabolic effect on the liver in adult patients (12) with metastatic carcinomas treated repeatedly to the toxic limits was insufficient per se to produce a cirrhosis-like picture.

The relative resistance of acute leukemia in adults as compared to children may be a reflection of:

- a) a reduced preferential requirement for the metabolite in the leukemic cells of adults as compared to the normal tissue cells.
- b) reluctance to induce a fully developed toxic state because of the increased danger of fatal hemorrhage in adults.
- c) a greater incidence of myeloid types in adults.
- d) a relationship of adrenal steroids and gonadal function in adults to the toxicity (12, 26) of folic acid antagonists.

Other Neoplasms: Transient tumor regression and some symptomatic improvement have been reported by many observers (24, 12, 26) in patients with lymphomas (Hodgkins' Disease, giant follicle lymphoma, leukosarcoma, lymphosarcoma and reticulum cell sarcoma) during treatment with folic acid antagonists. However, the effects were in general, less consistent and less predictable than would have been expected with other available chemotherapeutic agents.

In the chronic leukemias, a limited experience (26) with the antagonists has failed to disclose any advantage over other available methods of therapy.

The action of the antagonists on carcinomas and sarcomas has not been widely studied. In a few instances of metastatic breast neoplasm, transient regression of lesions was noted when the drugs were pushed to the limit of toxicity (12, 13, 27). Of considerable interest are observations of striking temporary regression of metastatic seminoma in adults, myo-sarcoma in adults (12) and children (28), and neuroblastoma (26, 29) in children. A more extensive study of the effects of these antagonists on a variety of human neoplasms may establish that certain additional histologic types respond temporarily during the folic acid-vitrofolium factor deficiency state.

Resistance: The development of resistance to chemotherapeutic agents has been observed among a wide variety of organisms including bacteria, molds, and protozoa. Recently, Law *et al.* (30, 31) and Burchenal *et al.* (32) demonstrated that leukemic cells subjected to the action of the antagonists during many serial transplantations ultimately develop resistance to the action of any of a number of folic acid antagonists. These studies were carried further until a state of dependence was produced. The dependent tumor cells actually showed retardation in growth (31) upon the withdrawal of antagonist or the administration of the normal metabolite (folic acid). It should not therefore be too surprising to observe the development of tumor resistance in man. However, the presence of pancytopenia in the peripheral blood, at a time when the bone marrow is full of blast cells, should not be taken as evidence of a resistant leukemia. The induction of peripheral blood or bone-marrow hypoplasia may be the first or only recognizable clinical sign of a deficiency state in such patients. Until convenient methods for detecting blood and tissue levels of both the metabolite and the antagonist are established, the adjustment of a dosage schedule for the patient will continue to depend upon criteria that are largely empirical, albeit formulated with a knowledge of the mechanism of action of the antagonists as observed experimentally.

Synergism. Among the numerous tumor-inhibiting agents available in the laboratory today, none show a wide separation of toxic from therapeutic action. Recently we and others have demonstrated (33, 34) that the toxicity produced by certain of these agents in combination may not necessarily be as additive as the therapeutic effect. For example, the combination of a folic acid antagonist and a guanine antagonist showed an enhanced anti-leukemic effect on the survival as well as on the tumor growth and bone marrow infiltration in mice bearing acute leukemia. Synergistic action has also been noted (33) between an acute karyoclastic and mitosis-inhibiting agent (alpha peltatin) and the folic acid

antagonists. It is a fervent but perhaps not unreasonable hope that a study of drug synergism will provide us with some basis for the development of a rational approach to the chemotherapy of human neoplasia.

ILLUSTRATIVE CASES

Case #1: A three and a half year old girl was admitted with a four week history of listlessness, fatigue, a lingering respiratory infection, anemia, jaundice, and hemorrhagic manifestations. Physical examination on admission to the Mount Sinai Hospital revealed an acutely ill, pallid, febrile child with generalized peripheral lymphadenopathy and numerous ecchymoses. The liver extended four centimeters below the right costal margin and the spleen to the left iliac crest. The peripheral blood leukocyte count was 4,900 cu. mm., of which

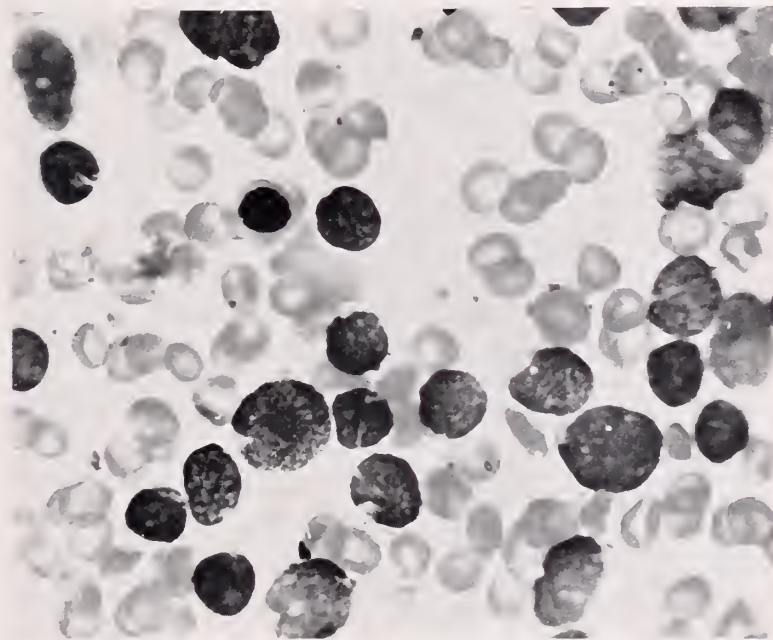


FIG. 3. Sternal marrow of Case #1 prior to treatment, showing monotonous one-cell type "blast" cell pattern.

92% were blast cells and 2% were neutrophils; the platelet count was 3,500 cu. mm. and the HB, 9.8 gms. The sternal marrow showed an increased cellularity and contained 96% blast cells (fig. 3).

Treatment with the folic acid antagonist, *a*-methopterin was begun at a daily oral dosage of 7.5 mgm. for five days. During this time the leukocyte count fell to 2100 cu. mm. but there were no other significant changes. Drug dosage was then reduced to five milligrams for the second five-day period. A slight increase in the number of neutrophils and platelets was noted at this time in the peripheral blood. There was no significant change in the differential cell count in the bone marrow, although slight changes in staining quality and in the size of the blast cells were noted. After the dosage had been again increased to 7.5 mg. daily for the third five-day period, the drug was temporarily discontinued to await the delayed development of an induced toxic state or evidence of a therapeutic effect. Three days after the antagonist had been discontinued the platelet count increased to 27,000 cu. mm. and seven per cent non-segmented neutrophils and nineteen per cent segmented neutrophils

were observed in the peripheral blood. A sternal marrow aspiration showed striking evidence of change (fig. 4) when contrasted with the pre-treatment state. There were 38% erythro-normoblasts, 36% distorted blast forms and 13% of myeloid forms in all stages of immaturity. This marrow was described as a "two-phase" marrow consistent with an incomplete or developing hematological remission. Six days after therapy had been interrupted, it was resumed again at daily doses of 7.5 mgm. This dosage was continued for eight days until an abrupt fall in leukocyte count from 2,500 to 650 occurred together with an exacerbation of fever without any evidence of oro-pharyngeal ulceration. Bone marrow examination (fig. 5) at this time showed an even more striking immaturity of the erythroid series than had been previously observed. There were 5% proerythroblasts together with numerous giant and bizarre myelocytes and metamyelocytes. Bizarre blast cells and basket

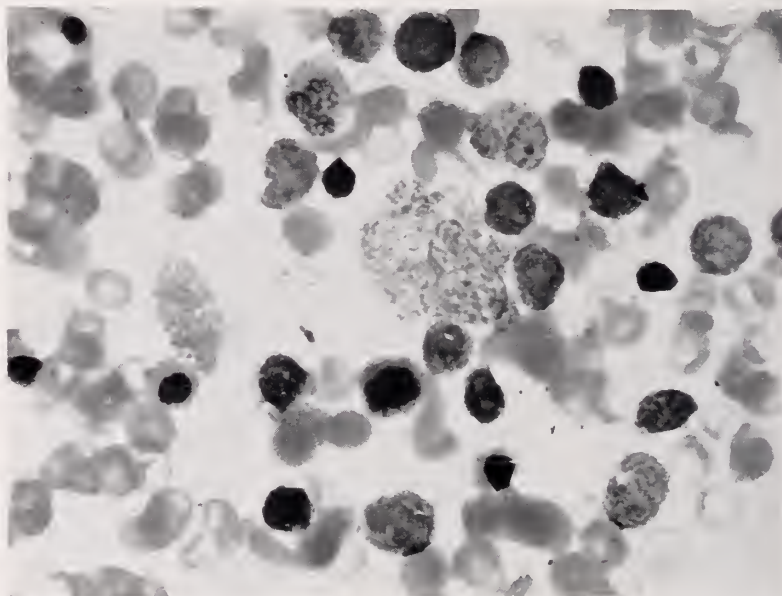


FIG. 4. Sternal marrow of Case #1 three days after treatment with 7.5 mg. daily doses of a-methopterin had been temporarily discontinued (a total of 100 mg. had been administered over a 15-day period). No definite signs of toxicity had yet developed. Note "two-phase" marrow with pyknotic hyperchromatic normoblasts, and the "washed out" bizarre blast cells and giant myelocytes.

blasts were also present, and much evidence of karyorrhexis and pyknosis. During the four weeks of therapy there had been progressive regression of lymphadenopathy and hepatosplenomegaly.

Seven days after the therapy had been discontinued because of the development of toxic signs, the fever and pancytopenia began to subside. Maintenance therapy with daily doses of five milligrams were therefore instituted. A complete symptomatic and hematological remission ensued. The patient was discharged with essentially normal marrow (fig. 6) and peripheral blood findings. To date a symptomatic and hematological remission has been maintained for four months while the patient has been receiving daily maintenance therapy. Partial alopecia developed as a late manifestation of drug toxicity.

Case #2: A seven year old white female was admitted to the Clinical Research Unit of the National Cancer Institute with fever, asthenia, and hemorrhagic manifestations of four weeks duration. Generalized lymphadenopathy, massive hepatosplenomegaly, anemia,

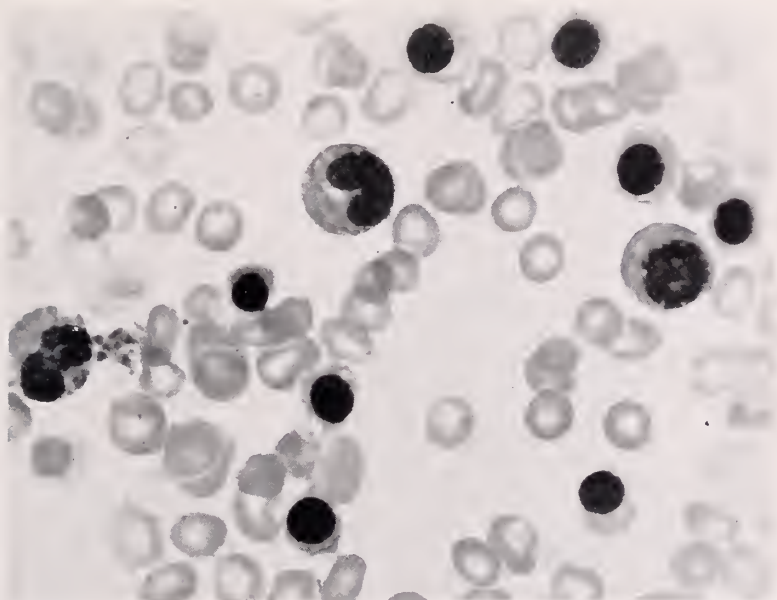


FIG. 5. Sternal marrow of Case #1 at the height of a clear-cut toxic (deficiency state). Note large numbers of normo-erythroblasts and the presence of myelocytes and metamyelocytes.

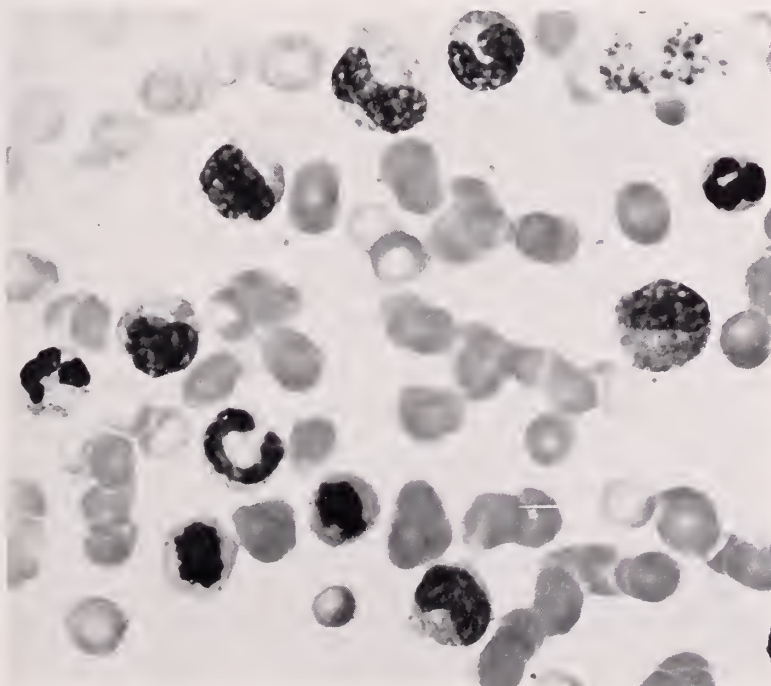


FIG. 6. Sternal marrow one week after previous illustration, showing late myeloid forms and the absence of immature blast forms.

and thrombopenia had been noted together with a leukocyte count of 22,000 per cu. mm. There were 98% blast cells in the sternal marrow and 45% in the peripheral blood. Prior

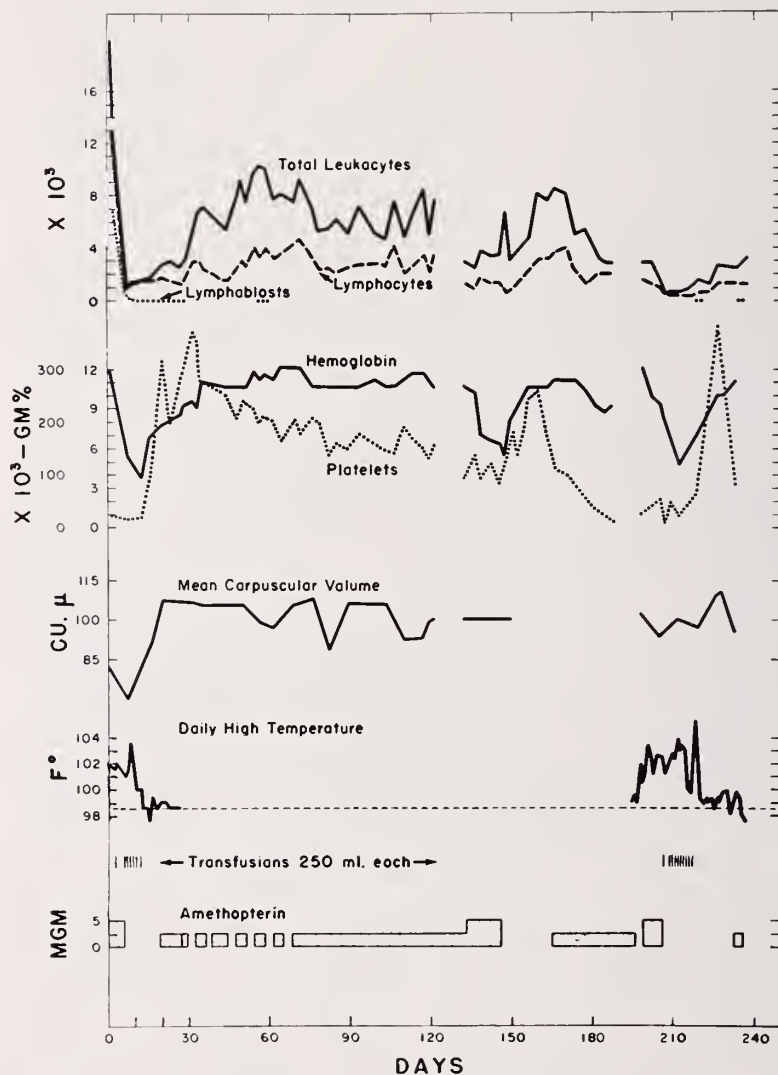


FIG. 7. Clinical data of patient with acute leukemia (Case #2). Three remissions were induced over a nine month period with dosage of 5 mg. of Amethopterin daily given for periods varying from 5 to 10 days. Symptomatic and clinical improvement preceded the hematological remissions which in each instance occurred from 5 to 10 days after these relatively large doses of antagonist had been stopped.

to admission, a short course of ACTH (15 mg. q. 6 h I.M. for four days) had failed to induce any significant hematological changes.

General measures including multiple transfusions were initiated (fig. 7) and amethopterin in 5 mg. daily doses was administered intramuscularly for five days. The leukocyte count fell rapidly and reached a level of 1000 per cu. mm. four days after the amethopterin had been stopped. A sudden increase in the platelet count occurred ten days (fig. 7) after the antagonist had been stopped and the mean corpuscular values increased to moderate

macrocytic levels. A steady rise in hemoglobin to essentially normal levels, together with complete regression in hepato-splenomegaly and amelioration of all symptoms then occurred. Three weeks after treatment had been instituted, the sternal marrow examination was interpreted as normal by the hematological consultant, Dr. C. Lockard Conley. Oral maintenance therapy with amethopterin at 2.5 mg. daily doses was begun and the patient was discharged to return to school and her usual activities. Three months later at the following-up examination, the spleen tip was palpated and slight reduction of platelets to the 125,000-150,000/cu. mm. level was noted. Macrocytosis and complete absence of blast forms was maintained in the peripheral blood. Four and a half months after initial treatment a further drop in platelet count, recurrent enlargement of the liver and spleen and an episode of broncho pneumonia occurred. Since the patient was not under our immediate supervision, her local physician was advised that this was presumptive evidence of an impending relapse. After recovery from the pulmonary infection amethopterin dosage was increased to five milligrams for a ten day period and then temporarily interrupted. Neither oral ulceration nor succinyl induction of thrombopenia or leukopenia followed but a rapid rise in the hemoglobin and platelets was observed. Maintenance treatment was again instituted but the clinical remission continued for only six weeks. She was re-admitted to the hospital with evidence of progressive hepatosplenomegaly, fever, pancytopenia, and an increased number of blast cells in the bone marrow. A third remission (fig. 7) accompanied by marked regression in bone marrow and visceral infiltration, was again induced by increasing the dosage to five milligrams, for a seven day period. Just prior to discharge it was noted that the patient showed a moderate increase in the serum globulin level, reduction in serum mucoprotein content, elevation of thymol turbidity and zinc sulphate tests, slight increase in serum bilirubin and the development of venous channels over the upper abdomen and lower thorax associated with slight edema of the extremities. It was believed that a cirrhosis-like picture was becoming manifest concomitantly with regression in visceral infiltration and induction of hematological and clinic remission.

The patient was discharged after instituting maintenance antagonist therapy at a reduced dosage of amethopterin (2.5 mg. per day). Three weeks after discharge and nine months after clinical onset of disease, the patient suffered a sudden fatal gastro-intestinal hemorrhage. From the microscopic examination of the organs it appeared that diffuse leukemic infiltration of bone marrow and viscera probably had developed during the brief interim after discharge from the hospital.

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TRIFACIAL (TRIGEMINAL) NEURALGIA WITH EMPHASIS ON ATYPICAL FORMS*

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One might assume that it should not be difficult to diagnose trifacial neuralgia—*tic douloureux*. Yet, one sees too often the condition in which both the physician and the dentist, with undue haste and not sufficient knowledge, consider a neurological disorder of the fifth nerve—or part of it—to be a true trifacial neuralgia. There should, and must be a distinction between the true and the untrue or the atypical type, since the treatment of one may be diametrically opposed to the treatment of the other.

The purpose of this discussion is to attempt to clarify some of the salient differences, in the hope that it will obviate the need of some distressing and, at times, mutilating operations.

To begin with, there is a fairly large array of related conditions, which cannot be clearly categorized. They may be borderline instances of atypical facial pains closely simulating those of the true trifacial neuralgias, but varying in distribution, radiation, or the nature and periodicity of the pain. This group, without a clear-cut diagnosis, is often very difficult to treat. Consultation between the neurologist, the otologist and oral surgeon is frequently requisite before a definite plan of procedure may be initiated.

Neuralgia, by definition, is pain along the course of a nerve—irrespective of the nature of the underlying causative process. Trifacial neuralgia (*tic douloureux*) is a form of neuralgia due to involvement of the gasserian ganglion and the roots and branches of the trigeminal nerve. At this point it may be stated that recent studies (1) indicate that by cutting and freeing the sheath of the 5th nerve root and gasserian ganglion, and not the nerve itself, relief of pain may be obtained, without loss of sensation. This may throw new light on the probable etiology of this disease in addition to certain advantages over methods previously employed in therapy. Reports of some clinicians indicate that 33.5 per cent of all cases of neuralgia are of the 5th nerve type (2).

The characteristic features of this disorder are quite well known. There is an acute painful spasm, paroxysmal in nature, seemingly related to pressure or some disturbance at the point of emergence of one or more of the peripheral branches of the trigeminal nerve. These areas are referred to as trigger zones.

Its etiology is basically unknown. No definite nerve pathology has been found. It has been reported by some that aneurysms, tumors and aberrant loops pressing on the trigeminal root have been observed in many cases (3). The pain is conducted along sympathetic or autonomic nerve fibers of the trigeminus. The motor root is never paralyzed (4). In the diagnosis of this disease, by virtue of the absence of any definite known etiology, consideration must be given to: a) focal organic factors; b) general or systemic factors, including predisposing causes.

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Among the focal organic factors, there are many worthy of note, such as:

1. Diseases of the maxillary antrum or other accessory nasal sinuses.
2. Pressure or infection due to nasal polyps.
3. Displaced or impacted unerupted teeth.
4. The various types of tumefactions involving either the soft or hard tissues of the jaws, the nasal tract or the adjacent structures.
5. Diseases of the teeth, the gingivae, the tonsils or the oropharynx.
6. Involvements of the temporo-mandibular joint.
7. Tumors or structural abnormalities of the gasserian ganglion or other parts of the 5th nerve.
8. Allergies.
9. Circulatory cranial disturbances.

Concerning the general systemic factors, one may consider the following as possible contributory or predisposing elements:

1. Age of the patient (usually occurs in mid-adult life or later).
2. Sex of the patient (females are more prone to affliction).
3. Diabetes mellitus.
4. Tabes dorsalis (where disease may be bilateral). (Total bilateral cases are estimated at being 4-5 per cent.) (5)
5. Syphilis—causing syphilitic basal meningitis or gumma implicating the 5th nerve in the floor of the skull.
6. Chemical sources—heavy metal poisoning (arsenic, etc.).
7. Anemia.
8. Gout.
9. Chill, exposure, fatigue, anxiety state and emotional shock.

The symptomatology, as already mentioned, is characterized by severe paroxysmal attacks felt in peripheral fields of the 5th nerve. These are intermittent in nature with little or no pain in between seizures. There are very few objective findings except for the appearance and behavior of the patient during an attack. The face is thrown into strong involuntary tonic spasm (fig. 1) on the affected side (6). It is accompanied by other phenomena such as flushing of the face, dilation of the ipsilateral pupil, excessive lacrimation, salivation and nasal secretions. The excruciating knife-like, lightning attacks of pain in the true form of neuralgia, is exclusively limited to all or part of one side of the face and, above all, to an area included within the normal anatomical limits of the 5th nerve. In between attacks there should be no pain—or only a slight dull ache not resembling that of an attack. Another characteristic is the so-called “trigger zones”. These areas at first appear as a single point, in which the pain originates, or is the point which, when stimulated, elicits an attack. It is usually found at the ala of the nose or on the upper or lower lip. However, it may be anywhere in the mouth or on the face or head which is supplied by the 5th nerve. In other words, the most common site of a trigger zone is at the areas of emergence of the peripheral branches, *e.g.* the infraorbital or mental nerves. As time progresses, secondary trigger zones may become more apparent. The simplest movements may precipitate a seizure. Acts like laughing, combing the hair, performing ablution, or even more gentle contacts such as the alighting of an insect on the

zone, the touch of a bed cover, or even a draft of air, have been known to precipitate an attack. Cold and dampness may be contributory. Patients become hyperconscious of these trigger zones and guard against touching or disturbing them in any manner, in fear of inciting a spasm of pain. In time the paroxysms increase in severity, acuity and frequency so that, on occasion, they may occur in such rapid succession that they appear to be almost continuous. In some instances the victim may develop a severe psychosis with suicidal tendencies, or become addicted to morphine (although it is said (7) that patients with this affliction are not helped by morphine). Since eating often precipitates trigeminal



FIG. 1. Appearance of face in a paroxysm of tic douloureux. Courtesy of C. V. Mosby Co., (*Jour. Oral Surg., Oral Med., and Oral Path.*, 4: 1417, 1951).

neuralgia attacks, patients may develop a fear of eating and, therefore, many manifest considerable wasting.

The marked facial distortion in the course of an attack is said to be the result of a central overflow of stimuli to the nucleus of the seventh or facial nerve.

There are no prodromal symptoms to an attack. It strikes suddenly and without warning. The most common areas of attack are the zones in the distribution of the 3rd, then 2nd divisions of the trigeminus. The ophthalmic branch is rarely affected.

The nature of the pain has been described as searing "like a hot iron", "pins and needles", paroxysmal, exquisite, lancinating, lightning, burning, stabbing, sharp and severe. It is, at any rate, always superficial—never deep or throbbing. The skin is not permanently affected and there is no change in its sensibility, however, except perhaps for some hyperaesthesia.

The primary concern of the clinician is to determine the true nature of the disease affecting his patient. The diagnosis, simple in many cases, is often beset with difficulty in view of the existence of some very similar disorders. Such neurological diseases as multiple sclerosis and tabes dorsalis may produce pain at times indistinguishable from that in true trigeminal neuralgia. Focal factors must be eliminated which may produce the so-called atypical trifacial neuralgias. These may include impactions, cysts, pulpal calcifications, tumefactions in the jaws, sinusitis, deep caries, retained root fragments, local osteitis, etc. In addition, there are several other types of neuralgia which may be confused with the major form—glossopharyngeal, sphenopalatine, infra and supra-orbital, etc. All of these usually will disclose their own typical areas of pain on careful examination.

Neuralgias have been classified by some as genuine (or idiopathic) as differentiated from symptomatic. In the former, no subdivisions can be listed since nothing definite is known about etiology. In the latter group are included infections, tumefactions, traumatic and constitutional causes. Although cases of genuine (or idiopathic) neuralgia should be diagnosed without too great difficulty, it is estimated by Frazier and others that at least 15 per cent of the cases are of the atypical type (symptomatic) (8).

It is important to note that paroxysms of true trifacial neuralgia do not last long—if they continue for long periods the case must be considered atypical. The pain of infraorbital neuralgia is at times felt superficially on the cheek below the eye and side of the nose; at other times it seems deeply situated “in the bones”. In true trigeminal neuralgia it is always on the surface.

It has been said that if there is demonstrable evidence of neurological or other definite physical signs or etiological factors, then the neuralgia is not true, but rather an atypical one. It is good practice to first attempt to eliminate such factors before a more radical step is decided upon. Sometimes herpes zoster may produce painful spasms without much evidence of superficial lesions. Frequently, patients plead for the removal of teeth, even though no evidence of pathology is demonstrable. (This, if acceded to can be very disappointing to both the doctor and the patient.)

Treatment. Palliative measures for *tic douloureux* are few and not too effective. Novocaine anesthesia may be employed to localize the offending branch of the nerve, and may be followed by an alcohol block in order to achieve relief of the pain for a longer period. This can be repeated on recurrence of the pain, but it is usually observed that the time intervals between the recurrent pains become shorter and shorter when alcohol block is employed, and hence the injection ultimately loses its value. Other methods include the inhalation of not more than 60 minims of trichlorethylene daily; amyl nitrate for its vasodilation effect; ferrous carbonate (1 Gm. *t.i.d.*); and the various vitamin therapies such as large doses of nicotinic acid, thiamin chloride, or pan-vitamin therapy.

The only lasting treatment, however, for the true *tic douloureux* is either peripheral nerve evulsion (removing a substantial length of the nerve) or more permanently, the retrogasserian ganglion resection. It is possible that the more recent procedure of decompression effectuated by cutting and freeing the sheath

of the root and the gasserian ganglion will prove more beneficial, in that relief of the pain is obtained without the loss of sensation.

Treatment of the atypical trifacial neuralgias requires careful study of the patient in order to discover the cause or causative factors involved. Once this is established, one then decides on the most adequate therapy. In those cases in which no definite factors can be found, one may be ultimately forced to proceed as in the true trigeminal neuralgia.

The following illustrate several cases in which diagnoses of trigeminal neuralgia were made by physicians and dentists. These were subsequently found to be instances of atypical trifacial neuralgias and responded to the removal of specific etiological factors.

CASE REPORTS

Case 1. This patient was a 48 year old negro woman, who entered the Oral Surgery Service of The Mount Sinai Hospital with a chief complaint of acute intermittent exquisite pain of the right face, radiating to the temporal region, of 4 years duration. Four years previous to admission, the patient began to notice sharp twinges of pain over the right maxilla which increased in severity and frequency as time went on. In several months the patient began to have excruciating attacks of pain over the course of the maxillary branch of the 5th and auriculotemporal nerves, sometimes once an hour. Some of these onsets were unprovoked while others seemed to arise after the patient washed her face, rinsed her mouth or performed other acts affecting the involved region. The patient then presented herself to an oral surgeon who diagnosed the case as trigeminal neuralgia and administered alcohol injections, with little improvement. She was subsequently examined and treated on the services of oral surgery and neurology at several hospitals. Various diagnoses were made involving several neuralgias and neuropathies and alcohol injections for the trigeminal and infraorbital nerves were again performed. Little relief was obtained and 4 years after the first onset of symptoms, the patient reported to this hospital's emergency ward and was sent to the oral surgery clinic. Here she gave a history of exophthalmic goiter and diabetes mellitus controlled by diet (10 years).

Examination: Eyes—extraocular muscles, negative; pupils react to light and accommodation: Fundi, normal. There is a large hematoma under right eye, the result of an infraorbital alcohol block given on neurologic service of another hospital.

Sinuses—right maxillary sinus not as clear as left to transillumination; tenderness over this antrum.

Mouth—a) teeth—maxillary right molars, 2nd premolars, canine and lateral missing; maxillary left 2nd and 3rd molars missing; remaining teeth showed mobility and some caries.

b) Gingivae—edematous and retracted,

c) Lips—dry, scaly with slight angular cheilosis,

d) Buccal surface of right maxillary ridge showed a small tender area of redness in the area of the 1st molar tooth.

Oral roentgenograms. In the area of the right maxillary 1st molar, a dense radiopaque object was noted lying near or in the floor of the maxillary sinus (fig. 2a). Further x-ray localization films showed this to be possibly a tooth root fragment (fig. 2b). However, careful questioning of the patient could not elicit recollection of any difficult extraction in this area nor the approximate date of extraction. This area also manifested an area of generalized rarification and loss of natural trabecular architecture extending to and involving the tuberosity.

During the history taking the patient suffered 2 severe attacks—each lasting about 30 to 40 seconds, during which she could do nothing but writhe in pain. Her facial musculature

contracted and distorted and her mandible quivered. The 2nd attack was elicited by pressing the red tender area overlying the antrum on the maxillary ridge.

It was decided to surgically remove the foreign body in the antrum and debride the involved area of the pathological bone.

Operative procedure: The patient was premedicated with $1\frac{1}{2}$ gr. of seconal and 300,000 units of aqueous procaine penicillin. Under 2 per cent procaine 1:50,000 epinephrine (posterior superior alveolar block and infiltration) anesthesia, an incision was made over the crest of the alveolar ridge from behind the tuberosity to the 1st premolar tooth. The muco-periosteum was reflected both buccally and palatally exposing an area of bone which was soft and pulpy to the touch of the curette. After this diseased bone was removed another x-ray picture was taken for further localization (fig. 2c) of the root fragment. Then the Schneiderian membrane was exposed, and the sinus presented a relatively normal appear-

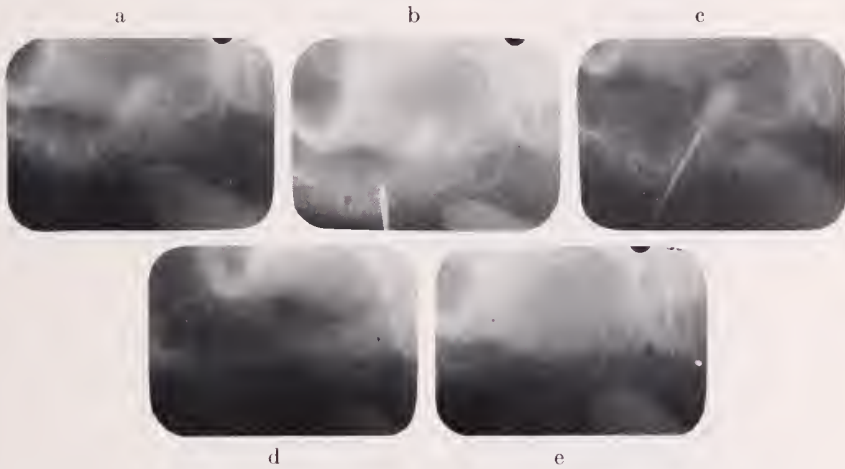


FIG. 2. *a.* X-ray film depicting root fragment lying at the floor of the antrum.

b. Film illustrating attempt at localization by means of the placement of a diagnostic wire.

c. Film illustrating the repositioning of the diagnostic wire, thus localizing, exactly, the position of the foreign body fragment, and helping to facilitate its removal.

d. Post-operative roentgenogram illustrating the absence of the foreign body.

e. Roentgenogram depicting a normal reparative process.

ance except for some granulation tissue which appeared on the antral floor. The root fragment which was lying on the floor of the antrum, imbedded in the Schneiderian membrane, was recovered. The antrum was then irrigated with warm physiological saline—sulfanilamide powder was dusted in, and the incision was closed.

The patient was given 100,000 u. crystalline penicillin with 300,000 u. of aqueous procaine penicillin and sufficient sedatives for a 24 hour period. Specimens were sent to the pathologist.

Postoperative course: The following day—the patient suffered only 4 attacks of pain of much less severity. The wound appeared clean and seemed to be healing. 600,000 u. of aqueous procaine penicillin were administered.

2nd day—2 attacks of definitely decreased severity—wound clean and healing well. 600,000 u. of aqueous penicillin given.

3rd day—2 attacks—mild in nature, wound healing well. 600,000 u. of aqueous procaine penicillin.

4th day—no attacks of pain—wound well healed, 300,000 u. procaine penicillin.

5th and 7th days—good progress—no further pain, 300,000 u. of procaine penicillin per day.

8th day—sutures removed—wound well healed. Postoperative roentgenograms taken (fig. 2d) showing interruption of Schneiderian membrane but clear sinus. Sinuses equally clear to transillumination.

One to two months follow up—patient feeling well and having no complaints. Wound completely healed (fig. 2e).



FIG. 3. Roentgenograms depicting three impacted or unerupted teeth, several retained root fragments and evidence of deep-seated caries.

Pathological reports: 1. Soft tissue from antrum acutely and chronically inflamed granulation tissue.

2. Bone—showing bony resorption, a vascular, fibrotic marrow with slight acute inflammation: chronic osteomyelitis.

At a subsequent date the root tip of the maxillary right canine was removed routinely.

Case 2. This patient had been examined by several physicians, including a neurologist and an internist, and all concluded that the patient, a white married woman, 55 years old, of slight build, was suffering from *tic douloureux* and advised retro-gasserian resection. One radiologist attempted x-radiation therapy without success. An alcohol block was unsuccessfully attempted. Then the patient was referred for relief (R. H. B.).

The patient manifested symptoms very similar to those of trifacial neuralgia. Her right

mandible was the site of involvement, and she appeared to have a trigger zone at the right mental foramen. However, there were occasional radiations, sometimes involving the right maxillary area, with twitchings to the eye.

Radiographic examination of the mouth revealed the presence of 3 impacted unerupted teeth, as well as several retained root fragments (fig. 3). Unfortunately, this patient was unaware of the presence of these factors even though she had been under treatment for her condition for some time by those who had previously seen her. Incidentally, there was one other factor to consider, namely, evidence of a marked traumatic occlusion. Some of the teeth were definitely depressed due to the excessive occlusal pressure.



FIG. 4. Diagram depicting the positions of calcific nodules (pulpal calcifications) within the pulps—in the pulp chambers or the pulp canals of teeth. These stones may cause pressure on the nerve fibrils of the pulp. (The arrows point to the stone formations.)

A. The pulp chamber (which contains, normally, the so-called nerve: nerve fibrils, blood vessels, and lymphatics).

B. A pulpal calcification (stone) (nodule).

C. The pulp canal.

Removal of the impactions and the root fragments, followed by balancing the occlusion with partial dentures resulted in elimination of the neuralgic symptoms.

Case 3. This patient, a girl aged 19 years, had been treated in two hospitals for a condition simulating trifacial neuralgia. However, the sharp lancinating lightning radiating pains manifested themselves bilaterally, and the trigger zones were inconstant. The attacks were spasmodic, on occasion lasting for a few moments, sometimes longer, but followed by complete cessation of pain. Codeine and morphine seemed to be ineffectual. The patient tried to commit suicide.

In both hospitals, unfortunately, a diagnosis of hysteria was made, but no significant etiologic factor which might have been helpful in the treatment of the patient was observed. The usual routine examinations were performed, including radiographic examination of the mouth, but nothing was recognized that might have even any remote bearing on the condition.

This patient had her full quota of teeth, well formed, and save for 3 tiny fillings, was

caries-free. The oral mucosa had a perfectly normal appearance, and visual examination of the mouth could very easily have been a misleading factor. Just prior to her being discharged from the hospital one of us (R.H.B.) was asked to examine the patient. Careful study of the oral radiographs revealed the presence of multiple pulpal calcifications (fig. 4). 17 teeth harbored calcific nodules in the pulp chambers or canals. Pulp stones, by virtue of their position (within a confined space) must create one of two conditions: 1. a compensatory atrophy of the pulp, as the stone or stones enlarge, or 2. a pressure on the nerve fibrils of the pulp, which can be transmitted to the nerve trunk or reflexly, elsewhere.

In this case, due to the multiplicity of the teeth involved, it was decided to remove the 17 teeth. (Devitalization of so many teeth in one mouth is not considered good practice.) After the teeth were eliminated, every vestige of the pain subsided, and failed to recur during a long period of observation.

DISCUSSION

The foregoing case reports represent merely a cross-section of a large number of cases of atypical trifacial neuralgias which are seen from time to time by both medical and dental practitioners who fail to observe some or all of the important details involved, and hence reach an incorrect diagnosis.

The first case (Case 1) clearly illustrates the necessity for a very careful and accurate diagnosis. This patient was seen and treated by others, unsuccessfully. Her pain originated from the involved area and radiated superiorly and laterally, from the infraorbital area, across the buccinator muscle to the tragus of the ear. The pain was superficial (not deep, as in the infraorbital neuralgias), but the attacks were excruciating, lancinating, and paroxysmal in nature, coming at its latest stage every 15 to 30 minutes, with complete remission between seizures. There were no objective signs or findings, except a faint tiny area of erythema with some tenderness over the area involved, intraorally. There was what appeared to be a trigger zone just beneath the molar prominence on the face. Pressure here, at times, would produce an attack, which might last for 30 seconds.

During the attacks, there was increased lacrimation and salivation but no cheek rubor. The patient violently clutched her cheek and went into tonic spasm of the facial and cervical musculature. The pain was limited to one side, and was not relieved by previous alcohol blocks of the 2nd or 3rd divisions. Morphine and other opiates apparently had no beneficial effect. The patient threatened suicide.

More than 12 months have passed since the patient was rendered pain-free, and there has been no recurrence, whatever. It is easily conceivable that some surgeons might have resorted to gasserian neurectomy in such a case.

The use of novocaine block anesthesia is often very helpful toward reaching a conclusive diagnosis. Sometimes alcohol block may be resorted to, and it may serve a useful purpose, even if its beneficial effect is not long lasting. It may help to confirm the diagnosis, and at the same time to familiarize the patient with the sensation of numbness of the involved parts. Thus the patient may decide whether or not to subsequently proceed with the avulsion or retrogasserian neurectomy for a more permanent relief, if we are dealing with a true *tic douloureux*.

Such neurological diseases as multiple sclerosis and tabes dorsalis may produce paroxysms of pain indistinguishable from true trigeminal neuralgia. Carcinoma-

tous and sarcomatous lesions may cause intractable pain, but these patients can usually be palliated. In the atypical neuralgias the intensity of pain may or may not be as great as in the true *tic douloureux*, but in the intervals there may be present a milder form of pain.

Since there is no specific etiology nor any significant neurological findings in this disease, some investigators believe that involvement of the teeth and jaws plays no role in the causation of true *tic douloureux*. Some attribute the cause to pressure on the trigeminal root due to tumefactions, aneurysms or arterial loops. Whatever the factors may be, it is incumbent upon us to carefully search for and to remove all possible local factors which may be contributory if not etiologic in character. Failing in this to obtain a beneficial result, the next course is obvious. Davidoff (9) states it simply as: "When correction of local conditions in the mouth does not eliminate sharp facial pain, a surgical cure with a very considerable assurance and without much danger to the patient may be recommended."

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ELECTRON MICROSCOPY AS APPLIED TO CARDIOLOGY*

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Since electron microscopy became a practicable method in science, time and again attempts have been made to use it as a tool for biological investigations. It is well known that the resolving power of the electron microscope is much higher than that of the light microscope, since the wave lengths used in the electron microscope are much shorter than those of visible light. The resolving power of each microscope depends on the wave length used in the microscopic procedure.

The fact that the electron microscope permits visualization of structures as small as macromolecules enables us to do basic new research in all fields to which this method can be applied. Among these, of course, the most important object for the cardiologist to investigate is the heart.

As great as the advantage of electron microscopy is in visualizing ultramicroscopic structures, its great disadvantage lies in the fact that only the smallest particles of tissue can be seen in each field of vision. Therefore, special techniques were developed to homogenize to the smallest fractions different tissues which were to be investigated. Subsequently, in order to obtain the clearest pictures of ultramicroscopic particles, metal shadowing of these very particles was invented (1, 2). Valuable as such a method is, it cannot tell us anything about the histological connection between the isolated particles in the tissue itself. It was therefore endeavored to develop electron microscopy to the higher level of electron histology by investigating material cut in adequate ways and in this way to determine the ultramicroscopic structure of a certain tissue (3).

The results of three years of investigations can be summarized in the form of the accompanying illustrations (fig. 1). Like the muscle fibers of the striated muscle, the muscle fibers of the heart are not the most primitive working units of this organ, but each such fiber of a diameter of 10 to 20 μ contains between 300-700 myofibrils of a diameter of about 0.2 to 0.5 μ each. These myofibrils are independent units connected to each other only by a Z-band-system which in itself is attached to the sarcolemma of each muscle fiber. In this way pictures were obtained showing a warp and woof pattern inside of the muscle fibers of the heart, the myofibrils being the contractile part of the engine, whereas the Z-band-system probably has the function of keeping the myofibrils in order and in addition to that it has a biochemical function. The Z-band-system is the part of the muscle fiber responsible for the visual impression of the cross striation and identical with the Z-bands of the striated muscle fibers, as they were first described by Dobie in 1849 and later on by Krause.

The place where the Z bands are attached to the myofibrils is characterized by the presence of their isotropic substance. In my opinion the existence of this substance is due to some activity of the Z-bands. The middle part of the myofibril between two Z bands is anisotropic, and it is there where the minerals are

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concentrated among which probably the potassium compounds play an especially important role.

Nuclei are present in the muscle fiber of the heart too. These are oblong and always surrounded by endoplasm. In adequately treated sections of the heart a very great number of small, partly submicroscopical bodies are always recognizable, which are arranged in long rows between the myofibrils. Such bodies for

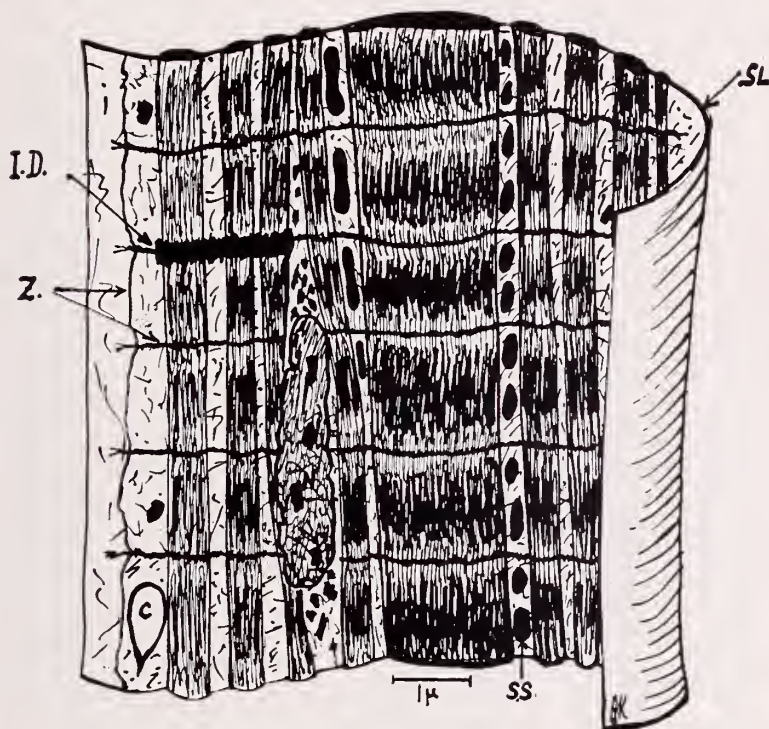


FIG. 1. Diagram of a muscle fiber of the heart. Sarcolemmic sheath (SL) cut open. Shown is only a part of the typical constituents of a muscle fiber of the heart. Attached at its ends to the sarcolemmic sheath is a network of the Z-bands connecting the different myofibrils. The latter are of different diameter, some of them ensheathed by intercalated disks (I.D.). Between the myofibrils, a nucleus (N) with 4 nucleoli, granulated material, at its poles. These nuclei never lie beneath the sarcolemma, but are imbedded between myofibrils. A capillary (C) enters through the sarcolemma and larger and smaller sarcosomata can be found between the myofibrils. Enlargement 10,000X.

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which the Swedish anatomist Retzius in 1890 introduced the name sarcosomes, as an abbreviation for sarcoplasmasomes, are also present in the fibers of striated muscle, but in smaller quantity. The sarcosomes have been known to anatomists for a very long time. W. Bowman already gave a description of these bodies in 1840 and Henle in 1841. Time and again they were observed mainly in insect muscles and in the heart muscle (4) of crustaceans and vertebrates. They never received any attention from cardiologists and only little attention from anatomists despite the fact that outstanding scholars like Biedermann, Knoll, Retzius,

Holmgren and others emphasized their normal existence time and again. However, some not less famous authors like Cohnheim, Hürthle, Krause and others regarded them only as disintegrated material of muscle fibers. It was also disadvantageous for the recognition of the importance of sarcosomes that until now

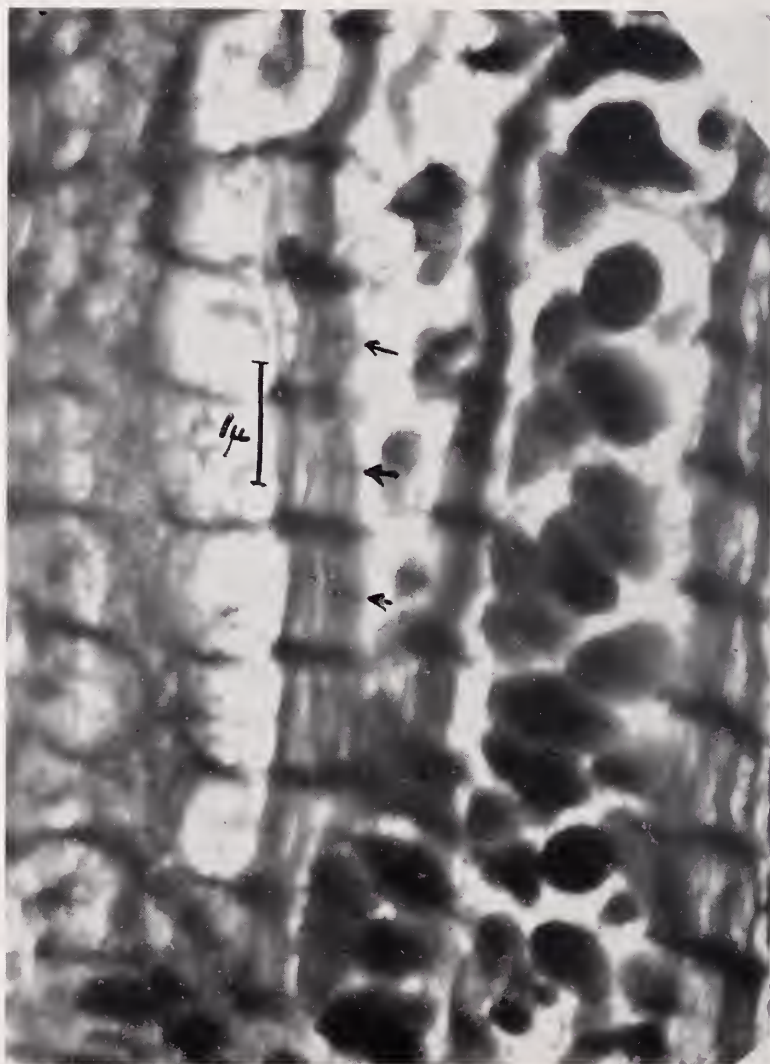


FIG. 2. Granulated sarcosomes between myofibrils of the heart of a mouse

nobody knew what kind of function to attribute to these particles in the sarcoplasm. The best decision that could be reached was the opinion of Holmgren and others that they are carriers of food material such as glycogen.

My own investigations concerning these bodies (3) brought an entirely new concept into the discussion based on the electron microscopic images. As the

pictures show (figs. 2 and 3), *different types* of submicroscopical bodies are distributed in the heart muscle between the myofibrils, some of ovoid shape, others of granular appearance and of spherical shape and still others band-shaped with an unquestionably strong resemblance to what is known as mitochondria in cells of other material. A great quantity of these sarcosomes though not all of them are arranged exactly between the meshes of the Z band system. That supports the idea that the Z band system is not only a passive net work to keep the myofibrils in order, but that it probably also plays a part in the formation of

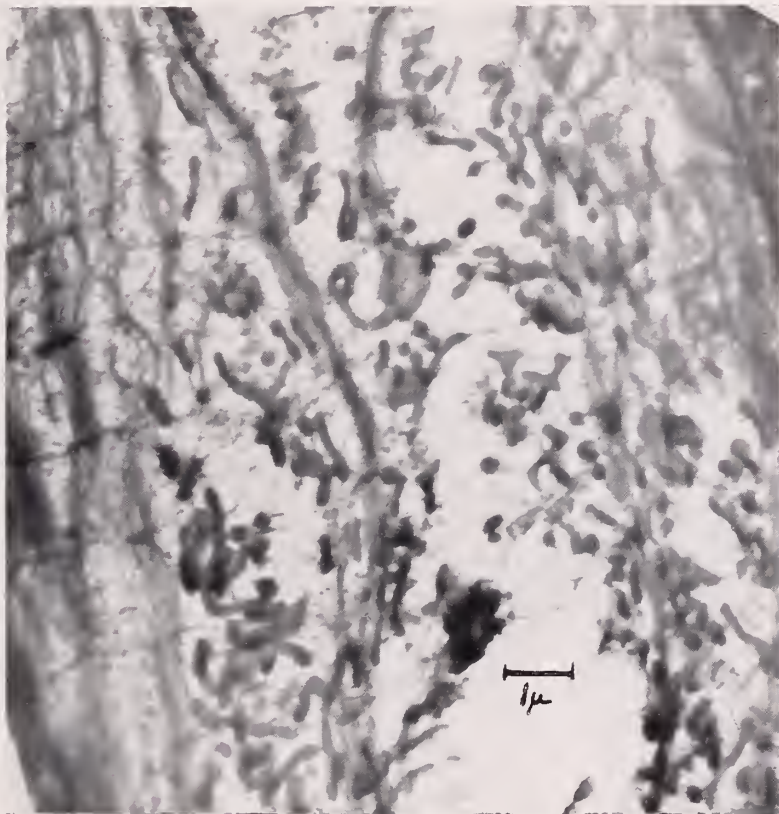


FIG. 3. Mitochondria between myofibrils of the heart of a mouse

sarcosomes, as it does in our opinion in the creation of the adjacent isotropic region of the myofibrils.

The only place, except for the heart, where according to previous literature, sarcosomes are found in great quantity and also closest to the myofibrils are the flight muscles of insects and of certain powerfully flying birds, as the dove (4). This makes it quite probable that the presence of these bodies is necessary for the steady, untiring activity of a muscle.

Since it was proven in the last decade that mitochondria in liver and kidney are the bearers of enzymes and vitamins (5), and since already in 1913 O. War-

burg was able to prove that certain granules of the liver are essential for certain oxydizing processes, the following concept concerning the function of the sarcosomes seemed justified (3, 4). Like in the liver and kidney, so in the heart muscle and in the flight muscles of birds and insects the sarcosomes present the place of enzyme concentration and vitamin concentration in the cell needed for a rapid restoration of the chemistry of the working muscle. The fact that these bodies are present in great amounts and nearest to the myofibrils and not only outside of the muscle fiber of the heart warrants a very quick and intense enzymatic effect, which gives the entire metabolism of this organ its characteristics and enables the heart to do strong and steady work.

A very important confirmation of this new aspect of the function of the sarcosomes of the heart muscle was given recently by Carroll Williams in Harvard University and his collaborators (6). They were able to show that the giant sarcosomes of the flight muscle of insects are really a place of concentration not only of cytochrome a, b and c, but also of different important enzymes too.

The above mentioned approach to the problem (3, 4), of course, opens new possibilities of investigation. It will be of importance to see whether the electron microscopic picture of the heart muscle, especially that of its sarcosomes, changes, for instance, in heart failure and in diseases in which we know that the heart muscle is seriously involved. The effect of cardiotonic drugs on the configuration and the amount of sarcosomes may be of interest. But of course now the most urgent task will be the biochemical investigation of the sarcosomes of the heart, just as the sarcosomes of the fly muscle of insects were biochemically investigated (6). Here the electron microscopic studies and their correct interpretation may lead to new progress in cardiology.

Another question which may now receive a different answer than before is the problem of electrocardiography. The hundreds of myofibrils encaased in one muscle fiber show that the generators of electromotive forces are primarily probably the myofibrils and it is not only necessary to take their existence into consideration in each theory of the electrocardiogram, but the following aspect has also to be considered. In a state of rest, there will probably be the same electric charge on each particle of the heart. This by electrostatic Coulomb forces keeps them in order and at a certain distance from each other. These forces must be quite high because of the very small distance of these particles, like sarcosomes and myofibrils, from each other. We do not know indeed when and where the first changes occur in the state of activation of the heart muscle fiber. They probably do not take place in the myofibrils, but somewhere in the sarcoplasm and that may lead to a different charge of the different elements of the muscle fiber, which in turn will produce an attraction of these various particles to each other and a close contact of the enzymes in the sarcosomes with the myofibrils.

It may be superfluous to indulge here in all the future possibilities resulting from these aspects. It was only my intention, following the kind invitation of the editor of this Journal, to show in an outline that even the small amount of work up to now done in electron microscopy of the heart leads to a waste field of histological as well as physiological investigations which may prove of importance for the clinical pathology of the heart.

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ABSTRACTS

AUTHOR'S ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL, STAFF

Members of the hospital staff and the out patient department of the Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

The "2-step" Exercise and Anoxemia Tests. A. M. MASTER. Med. Clin. N. America, 34, May, 1950.

The 2-step exercise electrocardiogram, a simple, safe, standardized procedure, is presented as an objective test of cardiac function. The importance of the test is emphasized by the fact that the resting electrocardiogram is normal in from 25 to 40 per cent of patients with organic coronary artery disease. The 10 per cent oxygen anoxemia test of Levy is presented as to method and criteria for a positive result. In our experience this test is positive in only 20 to 30 per cent of patients with organic coronary artery disease. The comparative value of the 2-step and anoxemia tests is discussed. The use of the 2-step exercise test for coronary insufficiency is advocated as a routine procedure in annual physical examinations, particularly for those undergoing excessive stress and strain, such as athletes, policemen, firemen and pilots, for earlier and more accurate diagnosis of cardiac disease.

Congenital Dextrocardia with Situs Inversus Complicated by Hypertension and Angina Pectoris. A. M. MASTER, L. PORDY, AND HAROLD S. ARAI. Cardiologia, 16: 300, May, 1950.

A case of congenital mirror image dextrocardia with complete situs inversus complicated by hypertension, coronary artery sclerosis and angina pectoris is presented. The resting electrocardiogram was characteristic of congenital dextrocardia with transposition of the cardiac chambers, with evidence of left ventricular hypertrophy and myocardial involvement. In this case the localization of the angina pectoris was over the right side of the chest. The single "Master 2-step" exercise tolerance test was positive, confirming the presence of coronary insufficiency on effort due to underlying coronary artery sclerosis.

Observations on the Clinical Use of Visamin (Khellin). R. H. ROSENMAN, A. P. FISHMAN, S. R. KAPLAN, AND L. N. KATZ. J. A. M. A., 143: 160, May, 1950.

The action of Khellin, a preparation derived from the fruit of an Egyptian plant, was investigated in patients with angina pectoris, *cor pulmonale* and bronchial asthma. The most striking results were obtained in *cor pulmonale* with improvement in color, exercise capacity and respiratory mechanics. Side effects, including nausea, dizziness, somnolence and diarrhea were frequent with the dosage used (100-300 mg. daily) and limits the use of the drug.

Hodgkin's Disease Involving the Stomach. HERBERT SANDICK. Gastroenterology, 15: 135, May, 1950.

Five of Hodgkin's disease involving the stomach are reported. The preoperative diagnosis was carcinoma of the stomach in all cases, and the diagnosis of Hodgkin's disease was made only after microscopic examination of the lesions. In 4 of the cases no generalized involvement could be demonstrated clinically or at operation. Two of these patients are asymptomatic 1½ years, and 7 years after subtotal gastrectomy. Another patient died of

incidental causes 6 years following subtotal gastrectomy without any symptoms referable to Hodgkin's disease, and without post-mortem examination. In the 4th case there is a recurrence of abdominal symptoms 5 months after operation. The fifth patient died 4 months after operation, and post-mortem examination showed diffuse cellular infiltration of the liver due to Hodgkin's disease with localized involvement of the spleen and diaphragm. The liver and spleen were not enlarged and were grossly normal except for a subserosal nodule of involvement in the spleen 3 millimeters in diameter. This case illustrates the fact that generalized Hodgkin's disease may become manifest by involvement of the stomach, and the generalization of the disease may only be discovered at post-mortem examination. One cannot, therefore, be certain in any living patient, that one is dealing with "isolated" Hodgkin's disease of the stomach. However, as long as this possibility exists, it would seem that gastrectomy is indicated.

A Rapid Method for the Determination of the Aureomycin Concentration of the Blood. S. S. SCHNEIERSON. *Proc. Soc. Exper. Biol. & Med.*, 74: 106, May, 1950.

A rapid method for the determination of the aureomycin concentration of the blood is described. The results of the test are completed and reported within five hours after the specimen is received in the laboratory. Sterile specimens and sterile technic are not required. The procedure is based upon the inhibition of the test organism, *Proteus vulgaris* OX-19 by the antibiotic, thereby preventing the reaction and color change produced in the urcaphenol red medium when urea is split to ammonia by the test strain. The minimum assayable level is 0.8 micrograms per ml. of serum. A high degree of correlation was found between the actual value and the results of assays with this method with 36 prepared specimens.

A New Method of Automatic Controlled Respiration. M. H. ADELMAN, R. A. BERMAN, AND A. S. W. TOUROFF. *J. Thoracic Surg.*, 19: 817, May, 1950.

Controlled respiration is an anesthetic technique ordinarily performed manually by the anesthesiologist in which apnea is induced and respiration maintained by intermittent inflation of the lungs. In the technique presented in this paper, respiration is maintained automatically by a simple mechanical device, the pneumatic balance resuscitator. This device consists of a differential pressure valve which converts continuous positive pressure into intermittent positive pressure. The anesthetic agent used is Pentothal sodium. Apnea is induced and maintained by the intravenous use of d-Tubocurarine. A detailed description of the anesthetic technique and clinical observations made on twenty operative cases is presented. The majority of the cases were transthoracic operations.

What Is New in Proctology. ROBERT TURELL, AND ALBERT S. LYONS. *Gen. Practitioner* 1: 27, May, 1950.

In this paper a review of the progress in all phases of anorectocolonic disorders of the preceding two years was presented for the general practitioner.

Islet Cell Adenoma of the Pancreas with Increased Insulin Excretion of the Urine. VICTOR WILLNER AND V. A. WEINSTEIN. *New York State J. Med.*, 50: 1103, May, 1950.

This is the case history of a patient with Islet Cell Adenoma of the Pancreas who for 5 years has been having attacks of confusion, restlessness, with loss of bladder control, followed by partial amnesia and relieved by intake of food. The positive findings at physical examination were a small uterine fibroid and the neurologic examination revealed absence of knee and ankle reflexes, sluggish response of abdominal reflexes, a positive bilateral Babinski with slight impairment of possession sense in toes and no change in vibration sense. Laboratory tests revealed fasting blood sugar of 40 mg.% which fell to 27 mg.% during hypoglycemic attack and went up to 62 mg.% one half hour after ingestion of a glass of orange juice. Stool examination revealed a 2 guaiac, many undigested starch granules, muscle fibres in moderate numbers and some fatty acid crystals, no neutral fats or soap were pres-

ent. Gastrointestinal series, barium enema and x-ray of gall bladder were negative. Duodenal pancreatic enzymes studies were done with secretin and revealed a normal external secretion of the pancreas. Urinary insulin concentration studies by the biologic assay method revealed insulin content of 1.55 units (24 hour specimen), normal average value being 0.18 units per 24 hours. On operation a small nodule was found near the tip of the tail of the pancreas. Hemipancrcreatectomy and splenectomy was performed and liver biopsy taken. Pathologic report was islet cell adenoma of the pancreas; spleen and liver normal. Patient made a quick recovery. Hypoglycemic attacks ceased completely and urine insulin concentration studies 2 weeks post-operatively revealed 24 hour output of insulin of 0.16 units. Sugar tolerance test two months post operatively was reported as normal. The following points are stressed in this case: (1) The importance of taking blood sugar level during hypoglycemic attacks in order to establish the diagnosis of hypoglycemia due to hyperinsulinism rather than depend on the fasting blood sugar levels which may be normal or never reach a level as low as those seen during the active episode. (2) The new approach to the diagnosis by determination of urine insulin output, (24 hour output).

Aerosols III. An Inspiration Time Meter for Quantitative Measurement of the Inhalation Period of Mists. H. A. ABRAMSON, H. H. GETENER, AND B. SKLAROFESKY. *Ann. Allergy*, 8: 307, May-June, 1950.

The device for measurement of the time taken for inspiring aerosols consists essentially of an electric circuit-maker which is activated by the back pressure that is set up when the aerosol is inspired. By this method (a) the total number of inspirations, (b) the average inspiration time, the total inspiration time, (c) the population distribution of inspirations, and (d) the ratio of the inspiration time to total time of respiration, are obtained. A typical experiment of lung clearance of phenolsulfonphthalein aerosol as a function of inspiration time is given. It is shown that within the limits of experimental error, there may be a linear relationship between the weight of dye excreted in 2 hours and the inspiration time between 200 and 400 seconds. By this technique it is demonstrated that under certain conditions approximately 15 to 20 per cent of dye clears the lung barrier and is excreted in the urine. Experiments on the production of histamine asthma with this technique provide a reproducible procedure for the induction of experimental asthma under semi-quantitative conditions and its control by therapeutic agents.

Some Studies on Basic Amines in the Blood under Physiologic and Pathologic Conditions. KURT ELIAS, AND HERBERT ELIAS. *Experimental Medicine and Surgery*, 18, Nos. 2-3-4: 89, May-August-November, 1950.

Blood levels of certain basic amines were investigated in 35 normal individuals under various conditions, and in 69 patients. No change in the basic amine content of the blood was demonstrated with age, sex, before and after smoking, during and after menstruation, but the levels were uniformly higher in fasting patients and in the upper limit of normal in 3 subjects on starvation-life-raft diet of 800 Cal/day. The normal range was found to be 0.15 to 0.30 mgm per cent with an average of 0.20 mgm per cent. Three untreated patients with Graves disease and one with thyroiditis had high basic amines with return toward normal under therapy. Myxedema likewise showed high levels with return to normal upon therapy. Liver disease, nephrosclerosis, diabetes and asthma showed high basic amine blood levels, while hypertensives, uremics and anemic patients showed normal levels.

Effect of Dibenamine in Chronic Simple Glaucoma. S. BLOOMFIELD, AND H. HAIMOVICI. *Arch. Ophth.*, 43: 969, June, 1950.

Dibenamine administered intravenously reduced the tension in each of 18 eyes with chronic simple glaucoma, many of which had not responded satisfactorily to cholinergic drugs. The necessity for the administration of dibenamine by slow intravenous drip and its pronounced systemic effects greatly limit the usefulness of the drug in the routine treatment

of chronic simple glaucoma. However, the hypotensive action of dibenamine in eyes with chronic developed group of effective sympatholytic drugs and may throw further light on the role of the autonomic nervous system in the pathogenesis of that disease.

Observations on a Small Outbreak of Infantile Diarrhea Associated with Pseudomonas Aeruginosa. A. L. FLORMAN AND N. SCHIFRIN. J. Ped., 36: 758, June, 1950.

A small, relatively mild outbreak of diarrhea associated with *Pseudomonas aeruginosa* (*Bacillus Pyocyaneus*) occurring on an infants' ward is described. The clinical course of five patients is given together with an account of the therapy employed. On the basis of encouraging results in one patient and reports of in vitro sensitivity of the organism, it is suggested that when other forms of chemotherapy fail, Polymyxin B be tried by the oral route. It is shown that washing a contaminated object in soap and water does not reduce the *Ps. aeruginosa* count, while soaking in 70 per cent ethyl alcohol for two minutes is effective. It is recommended that the procedure be included in the hospital technic for prevention of cross infections. Among twelve strains of *Ps. aeruginosa* studied for flagella antigens there were at least four serologic groups. The strains recovered from four of the five patients with diarrhea were serologically homologous and identical with the strain recovered from the hands of one of the nurses. The sole exception was the first patient whose organism was in a serologic group of its own. The sera of convalescing infants did not contain agglutinins for their homologous organism. Nevertheless some adult sera taken at random had agglutinins in moderately high titer for one of the strains associated with the diarrhea.

The Experimental Background and Clinical Use of Antibiotics. P. H. LONG, E. B. SCHOENBACH, E. A. BLISS, C. A. CHANDLER, AND M. S. BRYER. Lancet, 1: 1139, June, 1950.

The in vitro activity and pharmacology of the newer antibiotics are described. In addition, studies of bacterial resistance and the comparative results of treatment of experimental infections are discussed. In the light of this knowledge plus the cumulative experience of the group the comparative usefulness of penicillin, streptomycin, aureomycin, chloramphenicol and terramycin for various types of infection is presented. The study includes coccal, bacillary, spirochetal, rickettsial and viral infections. The dosage and dosage-forms as well as the common toxic reactions encountered during the course of antibiotic therapy are discussed.

Anoxic Effects on the Electrocardiogram Produced by the "2-step" Test. A. M. MASTER Bull. N. Y. Acad. Med., 26: 401, June, 1950.

Quantitative tests based on changes in the electrocardiogram induced by inhaling 10 per cent oxygen have been used to detect coronary insufficiency. Exercise produces similar alterations in the electrocardiogram in patients with coronary disease, and the "2-step" exercise electrocardiogram was introduced to standardize the effort. The similarity of changes seen in the electrocardiogram in spontaneous angina, during the "2-step" exercise test and, in the anoxemia test, indicates that myocardial anoxia or ischemia is the cause of these changes. When the 2-step exercise produces alterations in the electrocardiograms, coronary insufficiency and myocardial ischemia are present. In a comparison of the exercise and anoxemia tests, the former has been shown to be definitely the more sensitive.

Acute Coronary Insufficiency Due to Acute Hemorrhage: An Analysis of One Hundred and Three Cases. A. M. MASTER, S. DACK, HENRY HORN, BERNARD I. FREEDMAN, AND L. E. FIELD. Circulation, 1: 1302, June, 1950.

The occurrence of 59 cases of acute coronary insufficiency among 103 patients with acute hemorrhage, chiefly from the gastrointestinal tract, emphasizes the frequency and gravity of this generally unrecognized complication of bleeding. Clinical electrocardiographic and anatomic manifestations of myocardial ischemia and subendocardial necrosis are prone to appear in previously diseased hearts, although they may develop in otherwise normal hearts.

Consequently, prompt and adequate blood replacement is required in patients with coronary arteriosclerosis, enlarged hearts, valvular heart disease, etc., to prevent as well as to treat coronary insufficiency secondary to hemorrhage.

Observations on the Calorimetric Method for Measuring Digital Blood Flow. MILTON MENDLOWITZ. *Angiology*, 1: 247, June, 1950.

The calorimetric method for measuring digital blood flow has been re-examined critically and tested at every point for fallacies and sources of error. The overall maximum error is small. The normal range of variation after release of sympathetic nerve tone is sufficiently narrow to permit clear definition of the abnormal from the normal.

Recent Trends in the Diagnosis and Treatment of Varicose Veins. ROBERT S. NABATOFF. *Abstr. Surg., in Surg., Gyn. & Obst.*, 90: 521, June, 1950.

Notwithstanding many recent contributions in the field of varicose veins, there is as yet no universally accepted method of treatment. No matter what form of therapy is utilized, varicosities do occasionally recur. The fact that the disease is progressive in nature and that no specific etiological factor has yet been established, probably accounts for the failures in treatment. All recent articles containing constructive suggestions for the diagnosis and treatment of varicose veins are cited in such fashion that the latest refinements in diagnosis and therapy may become immediately apparent to the reader. A complete bibliography is provided.

Mucocellular Papillary Adenocarcinoma of the Lung Lobectomy, Five-Year Follow-Up.

KERMIT E. OSSERMAN AND HAROLD NEUHOF. *J. Thoracic Surg.*, 19: 875, June, 1950.

This is a five-year follow-up of a case reported in August, 1946, of mucocellular papillary adenocarcinoma of the lung treated by lobectomy. The purpose of the report was twofold: first, to set forth the distinctive microscopic features of the lesion, and second, the multilobular character and pronounced circumscription of the tumor, occupying most of the lower lobe. The patient had been under observation from the date of operation, November, 1944, to November, 1949, when the patient was 49 years of age and was symptom free. Physical examination was normal and roentgenogram of the chest was negative.

Angioneurotic Edema and Rash Due to Aureomycin, Reaction in a Patient with Multiple Sensitivities. A. D. PARETS. *J. A. M. A.*, 143: 653, June, 1950.

A case is reported in which aureomycin prescribed for early bronchiectasis produced a severe reaction in a patient known to be sensitive to penicillin, sulfonamides and butacaine sulfate (applied as a topical spray prior to bronchography). On the seventh day of aureomycin therapy, when 12 Gm. of the drug had been taken, periorbital edema developed, followed quickly by facial edema and a patchy macular rash; the latter began on the lower extremities and spread upward to involve the trunk. Antihistamines were of no benefit and the reactions that may attend aureomycin therapy. Sensitization during an initial course of the drug can occur.

The Effects of Vitamin E Administration Upon Diabetes Mellitus. HERBERT POLLACK, KERMIT E. OSSERMAN, M.D., JOHN J. BOOKMAN, MAX ELLENBERG, AND JOSEPH HERZSTEIN. *Am. J. Med. Sci.*, 219:657, June, 1950.

Newer therapies in diabetes mellitus require an evaluation based upon a thorough understanding of the natural history of development of this clinical syndrome. Numerous instances of spontaneous remission do occur in clinical diabetes. Twenty-seven patients with diabetes mellitus were selected for vitamin E therapy. These patients had been under observation in the metabolism clinic of The Mount Sinai Hospital from three to twenty-five years. Twenty-six of these patients were being treated with insulin. Thirteen of these pa-

tients were given the synthetic alpha tocopherol. The remainder received natural distilled mixed tocopherols. The dosage was 400 mg. daily. The administration of vitamin E, both natural and synthetic in dosage of 400 mg. daily, to known diabetics, whose previous fluctuations were well known, exerted no beneficial effect upon the insulin requirement or glycosuria.

Boundary Anomalies and Artifacts in Electrophoresis. MIRIAM REINER. J. Electrochem. Soc., 97: 213, June, 1950.

The anomalies inherent in the dissymmetry of the ascending and descending boundaries, with stationary boundary anomalies and interaction phenomena as well as electrophoretic spreading of boundaries are discussed. Artifacts due to convective and electrical disturbances are analyzed and the behavior and detection of false or spurious boundaries are considered.

Cor Biatritum Triloculare. BENJAMIN RICHMAN. Am. Heart J., 39: 887, June, 1950.

A newborn female, 3 days old, apparently healthy, suddenly developed dyspnea and cyanosis and expired within a few hours. The pertinent autopsy findings were: cerebral hemorrhage, a large right atrium, small left atrium, large interatrial septal defect and complete absence of the interventricular septum. Death was attributed to the cerebral hemorrhage. Despite the absence of the interventricular septum, multiple chest leads revealed a typical dextro and levo cardiogram on the anterior and posterior sides of the chest respectively. If the above finding is corroborated by further investigation, our concept of the origin and propagation of the cardiac impulse, as well as its expression in the electrocardiogram will have to be modified.

Lobectomy in a Patient Eighty-two Years of Age. M. B. ROSENBLATT, A. H. AUFSES, AND J. R. LISA. J. A. M. A., 143: 552, June, 1950.

This eighty-two year old patient had suppurative disease of the right middle lobe, which did not respond to antibiotic therapy. The sputum was examined by the Papanicolaou technique and was reported to contain malignant cells. Bronchoscopic examination showed only purulent exudate from the middle lobe bronchus and no evidence of tumour. Because of the possibility of the presence of a malignancy and the persistent suppuration, exploratory thoracotomy was performed. A middle lobe lobectomy was performed with uneventful recovery. Auricular fibrillation occurring postoperatively was controlled by quinidine. The surgical specimen showed only chronic inflammation and bronchiectasis with epithelium of the pseudostratified columnar type. The hazards of pulmonary resection in elderly patients have been greatly reduced by modern surgical technique and its adjuvants. Cells, which appear to be malignant in nature, may occur in the sputum of elderly patients with inflammatory pulmonary disease.

A Comparison of Cardiac Output Determined by the Fick Procedure and a Direct Method Using the Rotameter. ROBERT D. SEELY, WILLIAM E. NERLICH, AND DONALD E. GREGG. Circulation, 1: 1261, June, 1950.

Although the Fick procedure is accepted as a reliable technic for measuring cardiac output, it is basically an indirect method; and its accuracy has never been satisfactorily checked against a standard of established validity. Accordingly, in this investigation, experiments are performed in the anesthetized dog in which cardiac output is determined directly by measuring blood flow through the pulmonary artery with an optical rotameter, and output values so obtained are compared with simultaneously determined Fick values. Under the conditions of these experiments, comparisons show excellent agreement. The average variation between the two series of measurements is ± 5 per cent. Twelve of 13 comparisons agree within less than ± 8 per cent. This small deviation is within the range of error anticipated on the basis of known technical inaccuracies.

Administration of Research Programs in the Hospital. MARTIN R. STEINBERG. *Hospitals*, 24: 62, June, 1950.

Knowledge of the technique of administration, apart from any special research skill, gives the present-day hospital director an important responsibility in research programs. The article emphasizes that this holds true for hospitals of all sizes because research may no longer be viewed as the exclusive province of the larger institutions concerned with elaborating new techniques—it is, in addition, a stimulus to professional standards and morale and, indeed, has become a part of patient care. Dealt with in detail are administrative research problems such as the raising of funds, the translation of board policy into laboratory action, disbursal of funds and the maintenance of progress reports.

Liaison Psychiatry Pays an Extra Dividend. MARTIN R. STEINBERG, *Mod. Hosp.*, 74: 94, June, 1950.

A subtle but progressive change in the attitude of staff and personnel toward each other and toward the patient and his family and friends is the "extra dividend" the author sees evolving from Mount Sinai Hospital's comprehensive liaison psychiatry program. He credits the liaison psychiatrist, with his day-by-day demonstrations of the value of assaying and honoring the patient's personality, with furnishing momentum in the right direction concerning the staff's approach to its work. The article describes the development of the Hospital's psychiatric program and its therapeutic contributions.

Infectious Mononucleosis: With Hepatic Dysfunction, Thrombocytopenic Purpura, and Isolated Peripheral Nerve Palsy. R. S. WALLERSTEIN AND L. MADISON. *Am. Pract.*, 1: 624, June, 1950.

A case of infectious mononucleosis is presented in the course of which the following complications were sequentially manifest: hepatic dysfunction evidenced by liver function studies, thrombocytopenic purpura with widespread bleeding and a platelet count of 10,000 and an isolated median nerve palsy. The frequency and severity of each of these complications is discussed with review of the literature. One of them, the isolated median nerve palsy has not previously been reported though a more general central nervous system involvement is well known, though not common. The possible pathogenesis of the nerve palsy in this case is discussed.

Does Modified Measles Result in Lasting Immunity? S. KARELITZ. *J. Pediat.*, 36: 697, June, 1950.

A survey of approximately one third of the pediatricians in the United States and a large number of general practitioners was made to determine whether they had seen measles in patients who had previously had measles which was modified by convalescent serum, gamma globulin or immune adult serum. Only nineteen physicians indicated that they had observed that sequence in twenty-nine patients. Four doctors accounted for twelve of the total. Individuals with extensive experience in measles prophylaxis had observed this sequence rarely, perhaps once or twice or not at all. Data were obtained from the United States Public Health Service, New York City Health Department, American Red Cross and from pharmaceutical firms to determine the incidence of measles in the United States and the extent to which passive immunity was practiced. From these data it was established that there are approximately one million cases of measles a year in the United States and that several million children and adults have already been given passive immunity over a period of fifteen to twenty years. Since the incidence of measles is so great and the chance of re-exposure also very large, it is believed that many individuals who had had modified measles must have been re-exposed to measles subsequently. Since so very few cases of second episodes of measles were discovered it is concluded that modified measles renders a person immune in most instances for a long period, possibly for life.

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JANUARY-FEBRUARY

CONTENTS

	PAGE
OBITUARY—JOSEPH H. GLOBUS.....	iv
RECENT ADVANCES IN THE THEORY OF THE MECHANISM OF BLOOD COAGULATION. <i>Mario Stefanini, M.D.</i>	619
EXPERIMENTAL APPROACHES TO PSYCHODYNAMIC PROBLEMS. <i>Jules H. Masserman, M.D.</i>	639
THE EXTRACELLULAR COMPARTMENT: A COMPARISON OF THE CHLORIDE AND INULIN SPACES. <i>Louis B. Turner, M.D. and Marvin F. Levitt, M.D.</i>	653
PERFORATION OF THE PYRIFORM SINUS. A SEQUELA OF ENDOTRACHEAL INTUBATION. <i>Milton H. Adelman, M.D.</i>	665
CORRELATION OF DENTAL ABNORMALITIES IN HYPO-PITUITARISM. <i>J. A. Salzmann, D.D.S. and Stanley L. Wein, D.M.D.</i>	668
MYOMA OF THE SECOND PORTION OF DUODENUM. CASE REPORT. <i>Alvin A. Bakst, M.D.</i>	677
EPILEPSY AND THE ELECTROENCEPHALOGRAM. <i>Louis Greenstein, M.D.</i>	683
ABSTRACTS.....	689

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* Deceased November 19, 1952.

In Memoriam



JOSEPH H. GLOBUS, M.D.
November 25, 1885—November 19, 1952

JOSEPH H. GLOBUS

1885-1952

"What gives man lasting significance is not the accumulation he leaves behind, but rather the activity and zest that permeates his life and passes itself on to others."

Goethe

"Outstanding neuropathologist, neurologist, editor, writer, and grammarian; pioneer in the study of the morphology and clinical manifestations of brain tumors; founder and the moving spirit of the Journal of The Mount Sinai Hospital, to which he has given unselfishly and prodigiously of his time and talents. His fame as a teacher is widespread and his accomplishments as a clinician are assured, but the Journal will always remain a living monument to his untiring efforts in the Hospital's behalf."

Such was his colleagues' testimonial to Joseph H. Globus when, in April 1952, the Associated Alumni of The Mount Sinai Hospital designated him its "Man of the Year." It was a fitting tribute to this distinguished scientist and inspiring personality whose untimely death on November 19, 1952 interrupted a life truly filled with "activity and zest" passed on to others.

Joseph Globus was born in Vitebsk, Russia, on November 25, 1885, the son of Siphra Gos and Haim Globus, and the grandson of a renowned physician. It was apparent from his early years that medicine was to be his destiny. Emigrating to the United States in 1905, he plunged at once into a rigorous training schedule aimed at a career in medicine. To this end he applied himself unsparingly to the study of a new and difficult language, in the meantime supporting himself successively as steel worker, pharmacist's assistant and tutor. Overcoming seemingly insuperable obstacles, he persevered in his studies to win a B.S. degree from Columbia College in 1915 and the coveted M.D. degree from Cornell University in 1917.

Signs of early brilliance were recognized and rewarded, for while a student at Cornell he was appointed Lecturer in Anatomy. Following his internship at Montefiore Hospital, and further training in psychiatry at Manhattan State Hospital, he entered the United States Army as a First Lieutenant in the Medical Corps, serving from 1917 to 1919. At the conclusion of the war he began his life-long association with Mount Sinai Hospital when he became a Blumenthal Fellow in 1920.

In 1921, while completing his fellowship project in Germany, he met and married Grete Gans, his partner in a collaboration marked by great happiness and joint scientific interests. Three talented children, Rudo, Peter and Dorothy, resulted from this union.

Once established in his busy Neuropathology Laboratory at The Mount Sinai Hospital, he poured forth a steady stream of scientific contributions to his chosen field of endeavor; in all, over a hundred papers. These research efforts all gave evidence of meticulous preparation. Many represented noteworthy advances in neuropathology and neurology, for example his pioneering studies on the histo-

genesis of brain tumors; his system of classification of brain tumors, which served as a model for neurologists and neuropathologists throughout the world; his important work on spongioblastoma multiforme, cerebral aneurysm, infundibuloma and massive cerebral hemorrhage. These were scholarly contributions which did much to bring system and order into a confused area, an area of the greatest importance in medicine. The solid achievement of his scientific endeavors will endure.

Joseph Globus was Assistant Professor of Neuroanatomy at New York University from 1923 to 1927, Associate Professor of Neuroanatomy and Neuropathology at that institution from 1927 to 1939, and Assistant Clinical Professor at Columbia University from 1937 on. As a lecturer, he was a striking figure. He would enter the crowded amphitheatre ebullient, overflowing with enthusiasm. His lectures, carefully prepared, were models of lucidity and erudition, and into them he would pour his own zest and spirit, not without a touch of theatricalism, to make his abstruse subject come alive and remain full of infectious interest. To the hushed audience, his lectures were an unforgettable experience.

But first and foremost, Joseph Globus was a physician. Making rounds on the neurological wards, he stressed high standards of medical scholarship, yet did not sacrifice his feeling for the patient as a human being or lose any opportunity to interject some humane or philosophical sentiment. He gave of himself unstintingly as a physician, to all who needed his care and especially to the indigent.

In 1934 it was Joseph Globus who, despite his full career as clinician, investigator and teacher, undertook to found and edit the *Journal of The Mount Sinai Hospital*. Thereafter, and until his death, he was its guiding genius and made it known throughout the medical world. In 1942 he founded and edited the *Journal of Neuropathology and Experimental Neurology*, a journal noteworthy for its high standards.

Many honors came his way. He was awarded the Howe Medal of the University of Buffalo. He served as President of the American Neuropathological Association, President of the New York Neurological Society, and Chairman of the Section of Neurology and Psychiatry of the Academy of Medicine.

Joseph Globus was a man of single-minded purpose. When Harvey Cushing offered him an opportunity as neurosurgeon, when various institutions made available positions which would have lightened his many burdens, he never wavered from his chosen path. And yet, he always found time for the many young men who came to him to learn. He shared with them his knowledge and experience, he dealt gently and wisely with the personal problems they experienced, he opened wide the door to his home and his heart. One of these men, now Professor of Anatomy at a major medical school, recently captured part of his personal magic in the following words:

"It was to this man of great heart, open mind and scientific spirit, that I, twenty-five years ago, came to seek advice in a major decision of my life. The break I was about to make seemed impossible. How could it be done with all that was behind me? Like a kind father, Dr. Globus took me in hand

with the advice—‘stay here, wait, work, and think it over.’ Knowing that I loved scientific investigation, he immediately offered me quarters in his laboratory, suggesting a problem upon which both of us could work, and in a few days had me steeped in scientific research. In that humble laboratory at The Mount Sinai Hospital, below street level, day by day our friendship grew. . . .”

Honors and recognition he accepted with utmost modesty and simplicity, looking forward to things to be done rather than backward upon things accomplished. Happily, although he continued with his customary vigor to plan and work as investigator and editor, the last years of his life were serene. True, he was much concerned in later years about man’s inhumanity to man; he would rail upon occasion about the depersonalization of medicine and the superficiality of much modern “scientific” work. But he remained firm in the conviction that the full, rich potentialities of the human mind and spirit would some day be fulfilled and that this would be a better world for all to live.

Joe Globus, may your faith in mankind be realized, as you yourself brought this faith to fruition!

WILLIAM M. HITZIG, M.D.
for the Editorial Board

RECENT ADVANCES IN THE THEORY OF THE MECHANISM
OF BLOOD COAGULATION*

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Information on the mechanism of blood coagulation has been obtained chiefly through the purification of the single factors involved in the process and the analysis of their interreaction *in vitro*; and through studies of patients with bleeding tendency, when the effect of the deficiency of individual agents on the overall process of blood clotting may be investigated under conditions which are often unobtainable in the experimental animal. Thus, some of the phases of the process of blood coagulation have been reconstructed with sufficient detail. But, at the same time, difficulties have arisen, many of which are inherent to the complexity of the mechanism explored and therefore unavoidable. A few avoidable ones have also occurred. Individual investigators are prone to avoid comparison of their findings with the observations of others. While little value seems to be given by many to findings in bleeding patients, conclusions arrived at through studies in animals have been applied indiscriminately to the theory of blood coagulation in man. Characterization of the various factors "discovered" from time to time has been generally poor so that correlation of the data presented by various authors, although badly needed, appears to be at the present time an almost insoluble task. Finally, there have been frequent changes in the designation of various coagulation factors, on the basis of additional evidence on their nature and mechanism of activity. During the past ten years, however, the knowledge of the process of blood coagulation has advanced tremendously and the field is now followed with an interest which is, possibly, out of proportion to its importance in the broader mechanism of hemostasis. Reviews of the recent advances in this field (1) are apt to become obsolete quickly, at least in some points of detail, and, in view of the extreme disagreement and quickly changing ideas, their very usefulness may be open to question. This review is intended primarily for those who, although interested in the field, are greatly distressed and confused by the babelic multiplication of theories and individual factors which plague the subject of blood coagulation. It is intended to stimulate the clinician's interest and to facilitate the application to clinical problems of much accumulated theoretical knowledge.

A presentation of the theory of blood coagulation requires analytical information on the individual factors involved in it and on the mechanism and kinetics

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of their interaction. Factors believed to play a role in blood coagulation have been found in platelets, plasma and serum (table 1). Platelets supply a factor which is indispensable for the activation of thromboplastin (platelet thromboplastic factor), an agent which accelerates the formation of thrombin from prothrombin (platelet accelerator 1 or factor 1), one which accelerates the formation of fibrin (platelet accelerator 2 or platelet factor 2), and also a factor which

TABLE 1

Where the various postulated coagulation factors are found

(A) PLATELETS

1. Platelet thromboplastic factor (\rightarrow thromboplastin)*
2. Platelet accelerator 1 or factor 1 (prothrombin \rightarrow thrombin)*
3. Platelet accelerator 2 or factor 2 (fibrinogen \rightarrow fibrin)*
4. Platelet factor 3 (anti-heparin)

(B) PLASMA

1. Thromboplastinogen or plasma thromboplastic factor
2. Prothrombin (active, and (?) inactive)
3. Calcium
4. "Labile component"
5. "Stable component" (?)
6. Fibrinogen
7. Antithromboplastin
8. Antithrombin
9. Albumin X (heparin-cofactor)
10. Profibrinolysin
11. Antifibrinolysin
12. Kinase inhibitor (antifibrinolysokinase) (?)

(C) SERUM

1. All factors found in plasma (with the exception of fibrinogen), in concentration directly related to the extent of their utilization during the process of blood coagulation
2. "Serum accelerator"
3. "Stable component" (more active form?)
4. Metathrombin

* Into parenthesis it is indicated on which phase of the coagulation process a particular agent is postulated to be active.

opposes the anticoagulant effect of heparin (platelet factor 3). The last and the platelet thromboplastic factor are probably identical. Finally they release a vasoconstrictor substance (thrombotonin of Quick) which might be identified with serotonin, isolated a few years ago from platelets. Of all these agents, the platelet thromboplastic factor is of primary importance in the initiation of the clotting process. Plasma contains the plasmatic precursor of thromboplastin (plasma thromboplastic factor or thromboplastinogen), prothrombin, calcium, fibrinogen. Moreover, it supplies two agents which are apparently required for optimal conversion of prothrombin to thrombin: they are designated

in this review as "labile component" and "stable component." It must, however, be pointed out that the very existence of the "stable component" in plasma either as such or as a less active precursor is still open to question. Plasma also contains agents which oppose the coagulation process (antithromboplastin, antithrombin, albumin X or heparin co-factor), the proenzyme profibrinolysin, and possibly antifibrinolysokinase. Serum contains a) all factors found in plasma (with the exception of fibrinogen) in concentrations directly related to the extent of their utilization during the process of blood coagulation; and in addition b) "serum accelerator", an agent apparently derived from the "labile component" when thrombin or other product of the coagulation process acts upon it; c) "stable component" possibly in more active form than that found in plasma; d) metathrombin, a product of the reversible inactivation of thrombin by antithrombin. It is indeed possible that some of the factors supplied by the platelets might be identified at a later date with agents present in plasma and serum.

The nature and properties of some of the agents which have been mentioned have been carefully studied, particularly prothrombin, fibrinogen and "labile component". Many excellent reviews are available on the subject (2-5). Factors supplied by the platelets have also been fairly well characterized. Platelet factor 1 and 2 are obtained from the water soluble fraction of lysed platelets and platelet factor 3 from the insoluble residue of lysed platelets (6) (table 2). The platelet thromboplastic factor has many characteristics in common with both platelet factors 1 and 2 and especially with factor 3, and is chemically very similar to placental thromboplastin (7). Platelet factor 1 also shares many properties with the "serum accelerator" (serum Ac globulin), although the latter is more quickly destroyed at 53°C. and sediments when a solution containing it is centrifuged at high speed (32,000 rpm for 30 minutes) (8). The characterization of the "stable component" and of the plasma thromboplastic factor (thromboplastinogen) is thus far incomplete.

Evidence has been obtained in this Laboratory that an additional plasma component, distinguishable from plasma or platelet thromboplastic components, may take part in the activation of thromboplastin. The properties of this factor are very similar to those of the "stable component" and more careful work is necessary before the identity of the new factor is firmly established. Preliminary observations have shown that the deficiency of this factor is probably responsible for the hemorrhagic diathesis of two patients who exhibit prolonged clotting time of blood and deficient utilization of prothrombin during coagulation. These two patients cannot be distinguished from true hemophiliacs on the basis of clinical data and the usual laboratory tests, and have no familiar history of bleeding tendency. Their clotting defect may be corrected temporarily "in vivo" by the administration or, "in vitro" by the addition to their plasma of fresh platelet-free normal plasma or hemophilic plasma. Investigation is in progress to establish whether cases of "sporadic hemophilia" are not examples of the deficiency of the new thromboplastic factor, as apposed to cases of "hereditary hemophilia" in whom the deficiency of anti-hemophilic globulin is presumably the primary pathogenetic factor.

The greatest state of confusion has arisen in regard to the mechanism of the conversion of prothrombin to thrombin. Without doubt, calcium and thromboplastin play a physiologic role in this process. Moreover, two additional agents appear necessary for the optimal completion of this phase of the clotting process:

TABLE 2

Platelet factors active in the process of blood coagulation

(A) PRESENT IN THE WATER-SOLUBLE FRACTION OF LYSED PLATELETS (6)

Platelet factor 1 (Platelet accelerator 1)	(1) accelerates the conversion of prothrombin to thrombin
	(2) precipitated from solution by 50% saturation with ammonium sulfate
	(3) sediments from solution following centrifugation at 32,000 rpm for 30 minutes
	(4) heat labile (destroyed at 53° for 10 minutes)
	(5) non absorbed on gels
Platelet factor 2 (Platelet accelerator 2)	(1) accelerates the formation of fibrin
	(2) does not sediment from solution following high speed centrifugation
	(3) heat stable
	(4) absorbable on gels. May be eluted from them with sodium citrate solutions

(B) PRESENT IN THE WATER-INSOLUBLE FRACTION OF LYSED PLATELETS (6)

Platelet factor 3	(1) anti-heparin activity
	(2) suspendable in saline solutions
	(3) present in the insoluble and non-absorbable residue of lysed platelets

(C) PLATELET THROMBOPLASTIC FACTOR (7)

- (1) a lipo-protein
- (2) necessary for the activation of thromboplastin
- (3) insoluble in water, partly soluble in citrate phosphate buffer solution
- (4) heat stable (stable at 56°C.)
- (5) sediments when lysed platelets are centrifuged at 32,000 rpm for 30 minutes
- (6) has chemical characteristics similar to those of placental thromboplastin

Platelet thromboplastic component is the most important agent supplied by the platelets, since it appears indispensable for the initiation of the process of blood coagulation "in vivo" and "in vitro". Platelets also supply a vasoconstrictor principle, "thrombotonin", which has not been sufficiently characterized thus far (? serotonin).

the "labile component" and the "stable component". A large number of factors have been postulated, having some or most of the properties of either the "stable" or the "labile" components and have been given individual names. A list of them is presented in Table 3, with the understanding that many of these factors are, in effect, mixtures of prothrombin and either "stable" or "labile" component.

TABLE 3

Synonyms of various factors active in the coagulation of blood, demonstrated in man

A. FACTORS INVOLVED IN THE ACTIVATION OF THROMBOPLASTIN

Platelets thromboplastic factor	thromboplastinogenase (32) cellular thromboplastic component (7)
Plasma thromboplastic factor	prothrombokinas (33) plasmakinin (34) antihemophilic globulin (35) thromboplastinogen (32) thromboecytolysin (36) thrombokatalysin (37) plasma thromboplastic component (7)

B. THROMBOPLASTIN (TISSUES)

thrombokinas
cytozime (38)
thromboplastic protein (39)
thrombokinin (37)

C. FACTORS INVOLVED IN THE CONVERSION OF PROTHROMBIN TO THROMBIN OTHER THAN CALCIUM AND THROMBOPLASTIN

Plasma "labile component"	thrombogène (38) component A of prothrombin (40) factor V \rightarrow factor VI (41) accelerator factor (42) labile factor (43) co-factor of thromboplastin (44) plasma Ac globulin \rightarrow serum Ac globulin (14) proprothrombinase \rightarrow prothrombinase (2) prothrombinogenase \rightarrow thrombinogenase (2) ? prothrombinokinase \rightarrow thrombokinas (45)* plasma prothrombin conversion factor \rightarrow serum accelerator (1) proaccelerin \rightarrow accelerin (46)
Plasma "stable component"	co-factor V(2) ? component B of prothrombin (43) prothrombin accelerator (47) prothrombin conversion factor (48) prothrombin converting factor (49) co-thromboplastin (50) plasma precursor \rightarrow serum prothrombin conversion accelerator (51) proconvertin \rightarrow convertin (46) factor VII (9) ? inactive prothrombin (12) (see text)

* Meant to signify any agent capable of influencing the conversion of prothrombin to thrombin.

Many of the factors postulated in group (3) are very likely mixtures of "labile component" with prothrombin or, even more probably, of prothrombin with "stable component".

Some of the factors in group (3) are arranged in couples, joined by an arrow. Those at the right of the arrow are considered precursors and found as such in plasma; those at the left are considered the active (or more active) form and found in the serum. For this reason, some investigators prefer to think of "labile" and "stable" component as a system.

The designations of "labile component" and "stable component" are used throughout this review. They are not recommended for adoption since the overburdened literature has no need of new names, however logical they might be. They are used because they define one of the most important differential characteristics of the two factors and because they have proven of didactic value. It will be noticed that Table 3 does not contain a list of synonyms for prothrombin. This factor has escaped much of the confusion of the field and many of the al-

TABLE 4

Characteristics of the "labile component" and "stable component" of human plasma

"LABILE COMPONENT"

1. Influences the rate of thrombin formation and, possibly, also the total yield of thrombin
2. Present in plasma and, in much less concentration, in serum
3. Variably utilized during the process of coagulation of blood (see text for discussion)
4. Relatively heat stable (destroyed at 58° C.)
5. Very labile on storage, especially in the absence of calcium
6. None or little absorbed on gels and on Seitz and asbestos filters
7. Concentration in plasma non affected by Dicumarol administration or by vitamin K deficiency
8. When depressed, its concentration in plasma is not raised by vitamin K
9. During blood coagulation it is activated by thrombin to "serum accelerator"

"STABLE COMPONENT"

1. Influences the rate of thrombin formation and, possibly, also the total yield of thrombin (?)
2. Present in serum and, very likely, also in plasma (either as such or as a less active precursor)
3. Very resistant to heat and to many chemical agents
4. Very stable on storage
5. Absorbed on various gels, and it may be eluted from them with sodium citrate solutions
6. Quickly and completely absorbed on Seitz and asbestos filters
7. Concentration in plasma and serum promptly affected by Dicumarol administration and by vitamin K deficiency
8. When depressed, its concentration is quickly raised by vitamin K

It is evident that "stable component" shares many characteristics of the classical prothrombin (for the relationship of the two agents see discussion in the text)

ternative designations offered (prothrombase, serozyme, etc.) have fallen into disuse.

Table 4 summarizes the distinguishing features of "labile" and "stable" component. Both "labile" and "stable" component could possibly be considered more as systems than as isolated factors, since, during the process of blood coagulation, the "labile component" becomes activated to "serum accelerator" and there is yet unconfirmed evidence that the "stable component" is present as such or as a precursor in plasma and is changed to a more active factor during the process of blood coagulation. "Labile component" and "stable component" can be differentiated on the basis of their resistance to heat and storage, of their absorption on Seitz and asbestos filters and various gels, of the effect of Dicumarol adminis-

tration, vitamin K deficiency and vitamin K administration on their concentration. There is no doubt, of course, as to the reality on the "labile component", the dispute here being limited to its nature and mechanism of action. The recognition of the "stable component" is made very difficult by the great similarities of this factor with prothrombin. It does appear possible, however, to distinguish the "stable component" from prothrombin (9) since: a) "stable component" persists in serum long after prothrombin and "labile component" have disappeared from it; b) the concentration of "stable component" decreases earlier and more rapidly than that of prothrombin during Dicumarol administration; c) "stable component" is more rapidly absorbed on 30% asbestos filters than prothrombin. By somewhat simple methods it is possible to obtain a rather crude and incomplete separation of prothrombin, "stable component" and "labile component". Thus, normal oxalated or resin-decalcified plasma, repeatedly filtered through Seitz filters contains the "labile component", but no prothrombin nor "stable component". Normal aged native serum contains only "stable component"; aged oxalated or Amberlite IR-100 decalcified plasma of individuals treated with Dicumarol in massive doses for a few days contains a reasonable amount of prothrombin but not "stable component", which is drastically affected by the drug, nor "labile component" which disappears on storage. An incompletely purified preparation of "stable component" can be obtained from serum by a relatively simple method. Native serum is stored at room temperature, thus obtaining practically complete loss of prothrombin and "labile component". The serum is then decalcified by the addition of $\frac{1}{10}$ volume of sodium oxalate 0.1 M, and the calcium oxalate separated by centrifugation. The serum is now treated with $\text{Ca}_3(\text{PO}_4)_2$ 0.008 M which absorbs most of the "stable component". This can subsequently be eluted from the gel with $\frac{1}{15}$ M phosphate buffer at pH 8.2 or with sodium citrate 0.2 M and the salt separated by dialysis against repeatedly changed water. A similar process in plasma would yield a mixture of prothrombin and "stable component". With oxalated or Amberlite IR-100 decalcified plasma, repeated absorptions on $\text{Ca}_3(\text{PO}_4)_2$ 0.008 M will separate the "labile component" which is little or not at all absorbed, from "stable component" and prothrombin which are absorbed. The latter agents can then be eluted with sodium citrate. It is claimed that single filtration through 30% asbestos filters would retain most of the "stable component" and allow filtration of most prothrombin. While this may be true with ox plasma, it is not possible with human plasma to separate prothrombin from "stable component" by this method. In any case, it appears feasible to separate by simple methods the three agents, all of which present characteristic properties. Another point in favor of the individuality of "labile component", "stable component" and prothrombin is the observation that bleeding tendencies can be due to the deficiency of each specific factor. Deficiency of prothrombin and of "labile component" (of both congenital and acquired type) have long been recognized. At present, cases have been described in which a congenital bleeding tendency characterized by delayed prothrombin time is best corrected *in vitro* and *in vivo* by the administration of serum, which is poor in prothrombin and rich in "stable component" (10,

11). Patients of this type probably represent examples of "stable factor deficiency". Although sufficient evidence is accumulating in favor of the existence of such an independent agent, many questions still remain unanswered. It is yet to be established whether "stable component" is found in plasma as well as in serum and whether, in plasma, this factor is present as such or as a less active precursor. Also unsettled is the relationship of the "stable component" to the "inactive prothrombin" or "prothrombinogen" of Quick and Stefanini (12). The latter agent slowly becomes reactive prothrombin as plasma is standing; this phenomenon is responsible for the more rapid formation of thrombin and higher yield of the enzyme which is found when excess of "labile component" and thromboplastin are added to recently stored plasma, in the presence of calcium. Nor can we exclude the possibility that "stable component" could be prothrombin itself or a prothrombin derivative after thrombin (which has a smaller molecular weight than prothrombin) has been formed.

The fate of the "labile component" during the coagulation of blood is of great interest in the understanding of the process of blood clotting. While this proceeds, there is progressive diminution in activity of the "labile component" with progressively increased activity of "serum accelerator" (13).^{*} Also, if thrombin is made to act on plasma Ac globulin, serum Ac globulin develops (14). On the basis of these and other experiments, it is generally held, although alternative explanations are possible, that the "labile component" is activated to "serum accelerator." Thrombin is considered responsible for the activation, but how thrombin engineers this activation remains to be established. It might be asked whether "serum accelerator" and "stable component" are identical. A negative answer is suggested by the fact that "serum accelerator," unlike "stable component" is very labile on storage and the two substances have different extinction coefficients in the ultraviolet range.

As mentioned previously, sharp differences exist among various investigators particularly regarding the mechanism of the reaction of conversion of prothrombin to thrombin. Some authors incline to believe that prothrombin contains all the necessary materials for the formation of thrombin and that calcium, thromboplastin, "labile component" and "stable component" are "accessory factors" which influence only the *rate* of thrombin formation. The key experiment for this contention is the appearance of thrombin in solution of purified prothrombin in 25% sodium citrate (17). Some investigators have pointed out the weaknesses of this experiment while others believe, on the contrary, that the formation of thrombin from prothrombin is a stoichiometric reaction between prothrombin,

* "Labile component" activity of plasma and serum is determined through the ability of oxalated samples (after treatment with adsorbing gels which remove prothrombin and "stable component") to restore to normal the delayed prothrombin time of aged plasma (15). "Stable component" activity of plasma is determined through the ability of serum to shorten the prothrombin time of plasma with artificially reduced prothrombin content (16). In a given plasma, "stable component" activity can be determined by obtaining the clotting time of a diluted sample to which fibrinogen, prothrombin and "labile component" have been added in excess and comparing the result with that obtained with a normal plasma (9).

calcium, thromboplastin, "labile component" and possibly "stable component." This belief is based on the observation that no thrombin will form when one of these factors is absent from the reacting mixture. Failure to recognize the formation of minute amounts of thrombin could be responsible for this conclusion. What should be emphasized is that while experiments *in vitro* may indicate that most of the factors required for the optimal conversion of prothrombin to thrombin are fundamentally unnecessary and even interchangeable (2, 17), *in vivo* the deficiency to sufficient extent of any of the known factors is accompanied by severe bleeding manifestations, an indication that the hemostatic mechanism has become inadequate. From the point of view of human pathology, therefore, all the known factors of the coagulation process must be present and are to be considered indispensable for effective protection against hemorrhage.

While there is violent disagreement on this particular phase of the coagulation process, accord has been reached on other aspects of the problem. It is generally agreed that: 1) two fundamental reactions take place during the process of blood coagulation, the formation of thrombin from prothrombin and the formation of fibrin from fibrinogen; 2) there is also enough evidence in favor of a third preliminary phase consisting in the activation of thromboplastin. This would consist of the interreaction of a plasmatic factor (plasma thromboplastic factor, thromboplastinogen) and of a platelet factor (platelet thromboplastic factor). Without this preliminary phase, the process of coagulation of blood could not initiate; therefore such a conception emphasizes the primary role of platelets in the coagulation of blood. Even authors who deny the reality of the phase of activation of thromboplastin recognize that this agent is liberated from the platelets through the action of contact with foreign surfaces (such as lesioned vascular endothelium *in vivo* and wall of the test tubes *in vitro*) and that liberation of thromboplastin is indispensable for the initiation of the process of formation of thrombin. Plasma completely deprived of platelets and not contaminated by platelet products fails to clot altogether, even when all other factors of the clotting process are present in optimal amounts; 3) the coagulation process seems to proceed in two distinct phases, one slow, the other accelerated. The acceleration suggests the existence of an autocatalytic mechanism.

The fundamental agreement which exists among the various investigators concerning the phases of blood coagulation, with the exception of course of that of the conversion of prothrombin to thrombin, can be even better shown by the use of diagrams. Those presented here are through the courtesy of Dr. Errett C. Albritton and represent a most useful contribution to the field.

Dr. Errett C. Albritton, Editor of the Handbook of Biological Data, a publication of the National Research Council, some time ago requested certain investigators in the field to submit to him their concept of the process of blood coagulation. From the data obtained he prepared five schemes which are reproduced here with his permission, prior to their official publication. Data were submitted by Dr. Paul A. Owren, Oslo, Norway; Dr. Armand J. Quick, Milwaukee, Wisconsin; Dr. Walter H. Seegers, Detroit, Michigan; Dr. Leandro M. Tocantins, Philadelphia, Pennsylvania; and Dr. Mario Stefanini, Boston, Massachusetts.

In all schemes consideration is given to the anticoagulant mechanisms but the fibrinolytic system is excluded for simplicity and since it is generally held, with the limitations referred to in the latter part of this article, that it does not take part in the normal process of blood coagulation *in vivo*. The analysis of these diagrams allows one to visualize immediately which are the points of agreement and disagreement among the various investigators.

According to Owren, coagulation begins when thromboplastin is made available through tissue injury or through the release of prothromboplastin when platelets disintegrate by contact with a foreign surface. Prothromboplastin is then activated to thromboplastin also by contact, but in the presence of calcium and antihemophilic globulin. Thromboplastin, calcium convert proconvertin to convertin ("stable component") and with it they cause a minimal conversion of prothrombin to thrombin. This thrombin, while unable to cause any gelification of fibrinogen, is able to convert proaccelerin ("labile component") to accelerin ("serum accelerator"). When accelerin is activated, the interreaction of prothrombin, calcium, thromboplastin and convertin to form thrombin is greatly accelerated and thrombin is now formed in sufficient quantity to convert fibrinogen to fibrin. The fibrin clot itself, acting as a foreign surface, causes disintegration of platelets, release of prothromboplastin and an autocatalytic cycle is thus established (fig. 1).

Quick's theory is somewhat simpler. Thromboplastin is released by tissues or is formed by the interreaction of a platelet factor (thromboplastinogenase) and a plasmatic factor (thromboplastinogen). In a second phase thromboplastin, calcium, labile factor ("labile component") and prothrombin interreact stoichiometrically to form thrombin. Possibly an inactive prothrombin precursor (prothrombinogen) may be activated to prothrombin by the action of rough surfaces. The thrombin formed not only converts fibrinogen to fibrin but also "labilizes" platelets, determining the release of more thromboplastinogenase and, consequently, the formation of more thrombin. The fibrin clot exercises a very important function since by adsorbing thrombin it checks the ever accelerating formation of this enzyme which occurs during the coagulation of blood (fig. 2).

Seegers believes that platelet disintegration due to contact causes the release of thromboplastic agent (which reacts with antihemophilic globulin to produce thromboplastin) and two platelet accelerator principles. Thromboplastin is also yielded directly by injured tissues. Thromboplastin and calcium together with platelet accelerator 1 cause a minimum conversion of prothrombin to thrombin and this initial conversion starts the accelerator phase, namely the conversion of plasma Ac globulin ("labile component") to serum Ac globulin ("serum accelerator"). Thromboplastin, calcium, platelet accelerator, and serum Ac globulin cause accelerated conversion of prothrombin to thrombin. This enzyme together with platelet accelerator 2 converts fibrinogen to fibrin. Again fibrin checks the accelerated formation of thrombin by adsorbing the enzyme on its surface (fig. 3).

According to Tocantins, injured tissue releases thromboplastin and disintegrating platelets release thromboplastin and an accelerator substance. Thrombo-

plastin and calcium determine a minimal conversion of prothrombin to thrombin. This thrombin activates plasma Ac globulin to serum Ac globulin and the inter-reaction of this agent with thromboplastin, calcium and prothrombin causes greatly accelerated formation of thrombin. Thrombin converts fibrinogen to fibrin with the help of the platelet accelerator substance. Fibrin checks the auto-catalytic reaction by adsorbing thrombin while, at the same time, it causes further disintegration of platelets with release of thromboplastin factors (fig. 4).

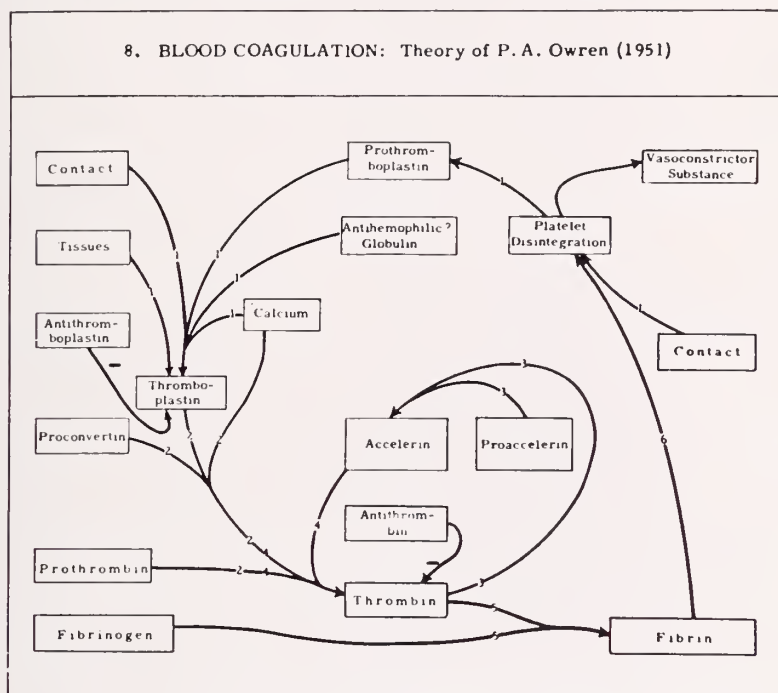


FIG. 1. The process of blood coagulation, theory of P. A. Owren (1951)*

A careful analysis of the four schemes presented indicates certain fundamental similarities and dissimilarities. As previously mentioned, disagreement involves the phase of the blood coagulation process in which prothrombin is converted to thrombin. Quick, to whom are due many of the most outstanding developments in the field, strongly insists that the formation of thrombin does not require the postulation of accelerator substances and that prothrombin, thromboplastin, calcium and "labile component" (labile factor) interreact according to stoichiometric proportions. In this he is supported by the finding that the "labile component" is quantitatively utilized during the coagulation of blood (18), although an accelerator can be demonstrated developing at the same time (13). Seegers and Tocantins postulate the existence of an accelerator system ("labile component" → "serum accelerator") and Owren postulates not only an accelerator

* Courtesy of Doctor Errett C. Albritton, Editor, the "Handbook of Biological Data," National Research Council, Washington, D. C., 1951.

unstable balance between positive and negative forces, which multiple substances can easily influence positively or negatively. All diagrams mention two anticoagulants physiologically present, antithromboplastin and antithrombin. Finally, all theories emphasize the concept that blood coagulation involves an autocatalytic reaction. Dr. Albritton has clearly presented this point by interpreting the theories of various investigators in cyclical diagrams. The autocatalytic mechanism in blood coagulation had not escaped the attention of early investigators (20),

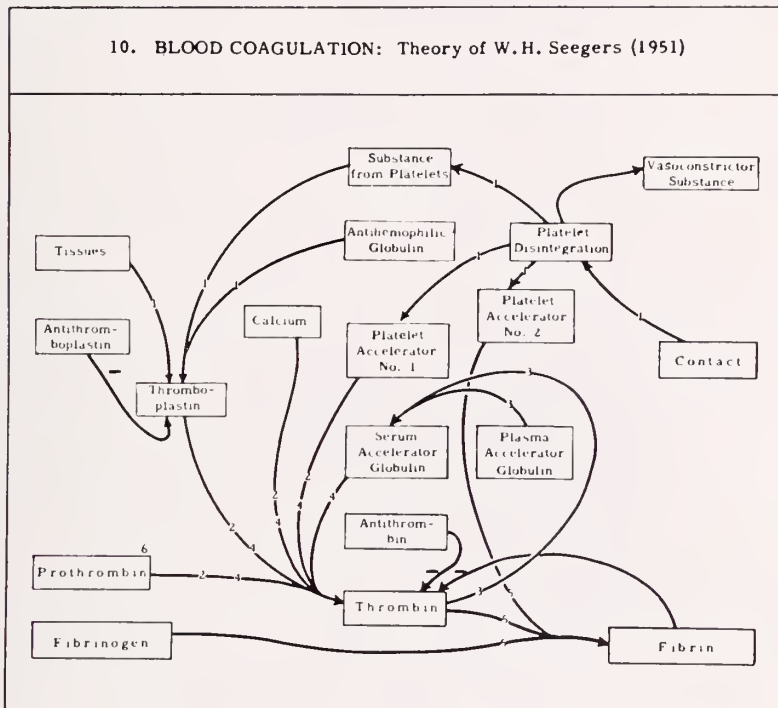


FIG. 3. The process of blood coagulation, theory of W. H. Seegers (1951)*

since it can be demonstrated with the help of an extremely simple experiment: the observation of the behavior of a sample of blood collected in a glass test tube and allowed to clot. At first no changes in the physical state of the collected blood are noticed; then, in a small fraction of time, the blood turns into solid state. It is evident that there must be a preparatory phase during which a product is formed which is able to greatly accelerate the conclusion of the process.

Whoever carefully studies the findings of other workers has the advantage of profiting from their experience. The writer, from his own investigations and those of others, and from attempts to correlate his findings with those of others, visualizes the process of blood coagulation in the following manner. Blood clotting can be divided into a "slow phase" and an "accelerated phase." The first initiates

* Courtesy of Doctor Errett C. Albritton, Editor, the "Handbook of Biological Data," National Research Council, Washington, D. C., 1951.

with the disintegration of platelets and liberation of platelet products and ends with the formation of a small amount of thrombin; the second initiates with the activation of the accelerator system and ends with the completion of the conversion of fibrinogen to fibrin. The first, fundamental step in the entire process, the clumping and disintegration of platelets, follows quickly any vascular lesion. Why a lesion of the endothelium determines clumping of platelets has never been satisfactorily explained. Once platelets are "labilized" or lysed, they appear to release a vasoconstrictor principle which can be found in the serum following injury of a vessel and is responsible for the prolonged generalized vasoconstrict-

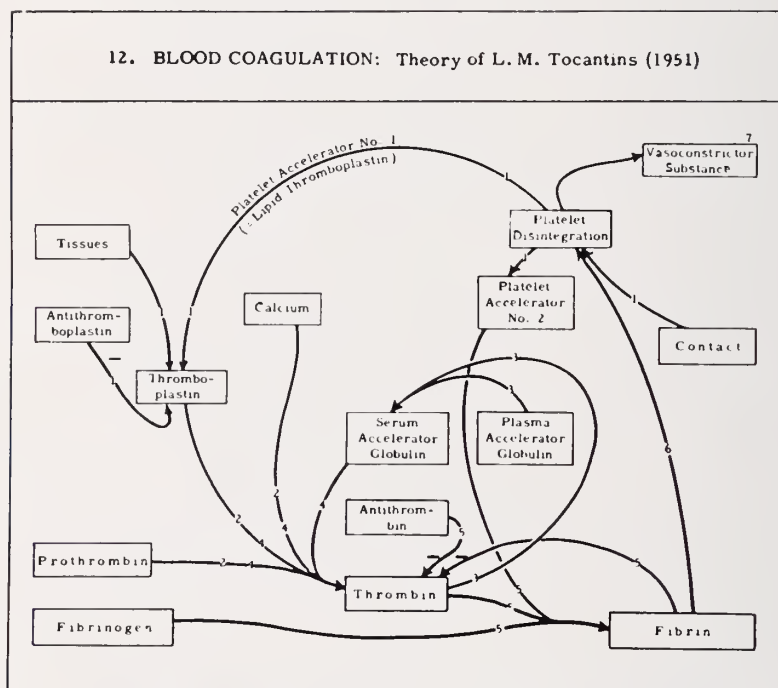


FIG. 4. The process of blood coagulation, theory of L. M. Tocantins (1951)*

tion which follows vascular injury (19). Moreover (and this emphasizes the central role of platelets in the process of hemostasis), platelet disintegration determines release of an agent which reacting with a plasmatic component determines formation of thromboplastin. It is possible also that platelets release directly a minimal amount of thromboplastin which, on the other hand, appears absent in red blood cells and leukocytes. The presence of a rough surface may be at this point responsible for conversion of inactive to active prothrombin, although this process *in vitro* is rather slow. Prothrombin, thromboplastin, calcium, the "stable component" and, possibly, the "labile component," interreact to form thrombin. Once thrombin has been formed, the "labile component" is "activated"

* Courtesy of Doctor Errett C. Albritton, Editor, the "Handbook of Biological Data," National Research Council, Washington, D. C., 1951.

into "serum accelerator." When prothrombin, calcium, "stable component," thromboplastin, "serum accelerator" interreact, the "accelerated phase" of the coagulation process is on and formation of thrombin proceeds at increasing speed. Once thrombin has been formed, it promptly converts fibrinogen into fibrin. At the same time, thrombin appears to be responsible for the mechanisms which produce the autocatalytic phase of blood coagulation. We have already discussed how thrombin will determine the "activation" of the "labile component" to "serum accelerator." Moreover, thrombin also produces clumping and disintegration

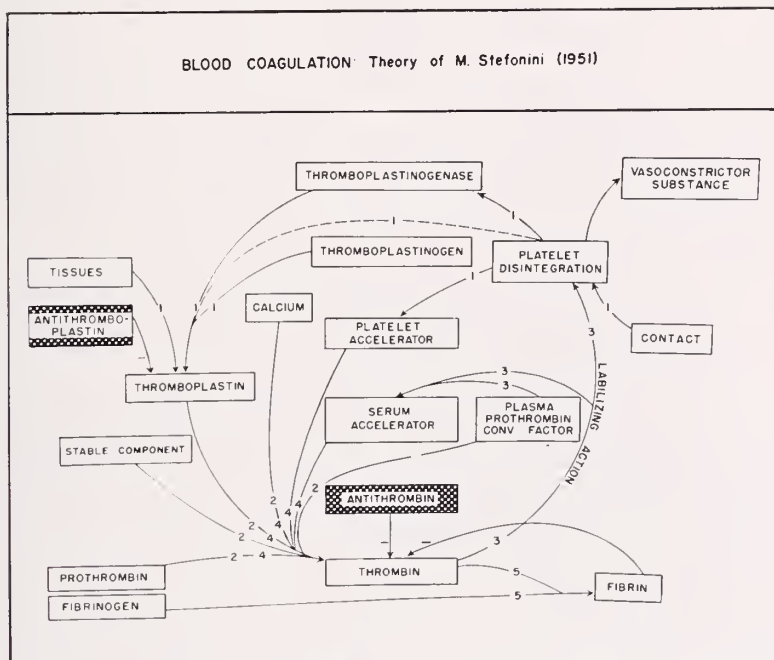


FIG. 5. The process of blood coagulation, theory of M. Stefanini (1951)* (modified)

tion of platelets at the site of its formation. This we have been able to show both by direct and indirect experiments (20). When platelets are lysed or "labilized" more thromboplastin precursor is liberated and an autocatalytic reaction is initiated (fig. 5).

It is obvious that such an arrangement is ideal for the prevention of bleeding. *In vivo*, the formation of thrombin is antagonized not only by the presence of natural anticoagulants, but, possibly even more, by the washing effect of blood which pours out of the wound. Even if this washing effect is somewhat decreased by the vasoconstriction caused by the liberation of "thrombotonin" (platelet vasoconstrictor principle), it would probably still be able to interfere seriously with the normal formation of a fibrin plug, were not the thrombin formed at ever

* Courtesy of Doctor Errett C. Albritton, Editor, the "Handbook of Biological Data," National Research Council, Washington, D. C., 1951.

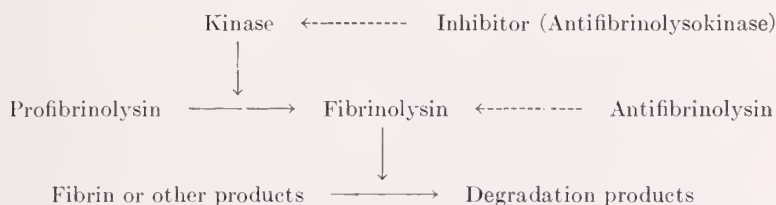
greater speed and in ever increasing amounts. The autocatalytic mechanism is, actually, so effective that it may even compensate for a limited deficiency of single coagulation factors. Patients with prothrombin activity of plasma as low as 20% of normal, with "labile component" activity as low as 25% of normal and platelet counts of 60,000–70,000/cu. mm. can still present apparently normal clotting mechanism and show good control of hemorrhage. On the other hand, such a process, if unchecked, could be very dangerous to life itself. Thrombin formation causing clumping and disintegration of platelets and this, in turn, breeding formation of more thrombin, a chain reaction could be established which would finally be interrupted by either complete intravascular coagulation through progressive extension of a thrombus (the surface of which is very rich in thrombin) or exhaustion of the supply of any of the factors necessary for the formation of thrombin, with irreparable damage to the organism. The anticoagulant mechanisms then become of significant importance for the well being of the individual, through their ability to control and finally to interrupt the autocatalytic formation of thrombin.

Little is known of the nature and the role of antithromboplastin and its very existence could bear better proof. Antithrombin is a globulin which interferes with the action of thrombin without directly inactivating it. It probably plays a significant role in many phases of the coagulation of blood and may be particularly important in the delicate phase when thrombin is formed in amounts insufficient to clot fibrin but adequate to "activate" the "labile component" to "serum accelerator." It has been said by many that antithrombin alone would not be capable of disposing of the thrombin explosively formed during the process of blood coagulation. An additional mechanism was postulated long ago on purely theoretical grounds and has been confirmed by the studies of Wilson (21) and later emphasized by other investigators (22, 23). The clot of fibrin itself cooperates with antithrombin in the control of the autocatalytic formation of thrombin. Fibrin is a large sponge able to adsorb great amounts of thrombin, thus effectively checking the autocatalytic mechanisms set in motion by this enzyme. Thrombin is again released when a fibrin clot reacts but at this time the enzyme is released slowly and antithrombin appears to be able to dispose of it. Albumin X or heparin-cofactor appears necessary for the anticoagulant effect of heparin, which is apparently a very complex one, antithromboplastic, antiprothrombic and antithrombic at the same time. It is still a moot question whether heparin plays any definite role in the normal coagulation process.

The fibrinolytic system is not included in the diagrams discussed. This is probably due to two main reasons. One is that this system is rapidly becoming the object of very specialized research needing individual discussion and one which appears to compete with the process of blood coagulation itself in complexity and interest (fig. 6). The second reason is that it is felt that fibrinolysin has no great importance in the physiological control of bleeding and is only rarely activated in pathological conditions. It must be said, however, that we do not know how much fibrinolysin and antifibrinolysin enter in the day-to-day regulation of the fibrinogen level. Also, since the release of tissue substances at the site

of vascular injury could be able to activate fibrinolysin, the role of this enzyme in the initiation of blood coagulation is probably worthy of careful investigation, especially since platelets exhibit fibrinolytic activity. Moreover, activation of fibrinolysin is known to be induced by "stress" and is one of the facets of the so-called "alarm reaction" (24) and thus may occur much more frequently than was previously thought. Finally, evidence is accumulating that ACTH, Cortisone and hormonal substances produced by the spleen play a significant role in the equilibrium of the fibrinolysin-antifibrinolysin system (25).

As studies with purified reagents *in vitro* and studies of patients with bleeding tendencies proceed, the time may be quickly approaching when a more complete understanding of the process of blood coagulation will become possible, and many of the controversies now raging among men active in the field will be settled. Another concept that may play an important role in the future of this field is the possibility that many of the factors active in the coagulation of blood may also possess other and even more important physiologic functions and attributes. It



Comment. Profibrinolysin(proenzyme)* is converted to Fibrinolysin (enzyme)† by a Kinase (activator)‡ found in tissues. The action of the Kinase is probably inhibited or antagonized by a number of inhibitors present in plasma and serum; that of Fibrinolysin by Antifibrinolysin,§ present in plasma and serum. Profibrinolysin and fibrinolysin are found in plasma and serum.

FIG. 6. The fibrinolytic system in human blood

is difficult to escape the conclusion that many of the agents of the coagulation process are present in amounts that greatly surpass their greatest anticipated need for the control of hemorrhage. Moreover, the turnover of proteins involved in the process of blood coagulation is rapid, indicating the prompt utilization of those materials by the body. Thus, all tissues and especially the lung contain amounts of thromboplastin obviously in excess of the requirements of hemostasis. Heparin, considered as an anticoagulant only, has now been proven to have a possibly much more important role as a regulator of the equilibrium of the various lipid fractions of the blood (26). One of the factors intervening in the conversion of prothrombin to thrombin (possibly the "stable component") is suspected, but not proven, to be the hemolytic factor responsible for the destruction of red blood cells in paroxysmal nocturnal hemoglobinuria (27). When its concentration is depressed by the administration of Dicumarol a striking reduction of hemolytic activity is promptly noticed (28). Fibrinogen, again in great excess of the hemo-

* Plasminogen, tryptogen, prolysin, lytic factor

† Plasmin, tryptase, lysin (tissues)

‡ Fibrinolysokinase, fibrinokinase

§ Antiplasmin

static needs, may play a role as the building stone of hematopoietic tissue. This has been suggested by experiments of Whipple *et al.* (29) in dogs. The writer, when in India, had the opportunity of observing a series of cases of tropical sprue treated with liver extract. The onset of hematologic recovery, as indicated by the elevation of the reticulocyte count, was accompanied by peripheral edema and drop in the total protein level in plasma. A similar observation has been reported by Das Gupta and Chatterjea (30). The concentration of fibrinogen in plasma was also strikingly affected. Whether increased production of hemopoietic tissue is also responsible for the fibrinopenia which is characteristically found in severe cases of polycythemia vera is being investigated at present (31).

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EXPERIMENTAL APPROACHES TO PSYCHODYNAMIC PROBLEMS*

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HISTORICAL REVIEW

Until recently, psychiatry in general and psychoanalysis in particular were usually defined as "sciences devoted to the study and treatment of diseases of the mind." Currently, however, many pragmatically minded thinkers and investigators are questioning this glib definition somewhat more closely. What, to begin with, *is* "the mind"? Is it the supraorganic expression of some ineffable "soul" vouchsafed only to human beings? Is it a composite of "faculties", of psychological abstractions vaguely named "instincts", "emotions" and cognitions, or of topographic subdivisions called, "id", "ego", "superego", etc.? Or is the mind, after all, only a categorical term used to summarize the totality of a person's observable visceral and neuromuscular *behavior*? But if the last definition comes closest to being operationally meaningful, how can we speak of the mind as being "diseased"—or do we mean by "mental disease" merely that one person judges whatever he can observe of the behavior of another to be grossly inappropriate for the contingencies of time, place and culture? And even so, why did the subject behave—and the observer judge—as they did?

MYSTICISM AND MAGIC

Questions such as these must have troubled men long before they were able to approximate them in words; at any rate, our ancestors seem to have reiterated the same blind, groping and self-delusive answers to them down the ages. Primitive man, fearfully close to the stark realities of helplessness, loneliness and the ever-present threat of suffering and death, developed perhaps man's most deeply rooted defenses against these anxieties: first, the cherished premise of his own invulnerability and immortality; second, a glorification of sexuality as affording him enraptured moments of trustful reunion with another human being in the quasi-deistic act of procreation; and third, the wishful belief that he could likewise, through magic thoughts, words and rituals, assert his omnipotence over the very Gods of the Universe themselves. So basic are these fundamental self-delusions of humanity that they are immanent in nearly all of our customs, our cultures, our religions—and our philosophic and psychologic rationalizations about our own behavior. First; perhaps, came the rites for controlling the Givers of Food and Shelter, such as the totemization of game-animals and the worship of primal mother symbols (incidentally, we still put cocks on our spires, and arch our door-

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ways or tack horseshoes above them to honor the cornucopic womb of Isis). Almost immediately, too, there developed both the sacred and profane adulation of the sexual orgasm and of the powers of parenthood—man's only thaumaturgy potent enough to deny suffering through ecstasy and to conquer death by engendering life anew. And certain it is that at the very dawn of recorded fantasy man was also creating gods who, in the image of glorified and all-powerful parents would protect, cherish and serve him as he wished.

And here also, as man's imagery grew, were ready-made "explanations" of his own behavior. Obviously, he both controlled *and was controlled by* various categories of gods: those of bodily lust (Dionysos, Loki, Ahriman, Siva and all the other dark and cloven-hoofed ancestors of our Devil); those of reason, compassion and light (Apollo, Thor, Ahura-Mazda, Brahma and other gentle demi-gods who lived in the guise of men and helped them deal with the realities of this world as well as the putative next) and finally, the supreme and sublimely indifferent Givers of Universal Law: Zeus, Wotan, Yahweh and their imperious ilk. These seemed to play with men as pawns, but even so indomitable Man could alter his fate by threatening, cajoling or bribing the very divinities he created in heaven and himself represented here on earth.

DIAGNOSTICS AND DYNAMICS

These, then, were man's first wishful rationalizations of his own conduct. But, as August Comte pointed out, though all sciences begin with mysticism, they generally develop through two other theoretical phases, namely: the taxonomic and, finally, the dynamic. Psychiatry, about two centuries ago began to concentrate on the second of these phases through the observation and classification of human behavior. Of course, man's first observations of the complexities of his own conduct were predictably biased and inaccurate, and his classifications often arbitrary and dogmatic; indeed, even today we are prone to survey each other with a defensive clinical stare and the covert appraisal: "compared to me, thou art a "narcissist," a "neurotic," a "cyclothyme" or some other deviate with an even more resoundingly condescending appellation.

It would be tempting to round out this fragmentary introduction by assuming that in modern times psychiatry has at last left such rubrics behind and is now a truly scientific discipline devoted to a dynamic understanding of man and the application of rational methods for readjusting unhappy deviations from the golden norm. As psychiatrists we wish this were completely true, and yet we must admit that all about us are residues of mysticism and irrational dogmatisms in our field. Without adequate diagnosis or rationale, too many patients are still being partially burned or suffocated to cure their "mental illness" (*ex evilness*)—a source of future regret even though the electrical *auto-da-fe* is now confined to the brain under the guise of "shock therapy", whereas the Inquisitorial suffocation is scientifically yekept "carbon dioxide inhalation treatment." And even in the relatively enlightened spheres of psychiatry there are relics of mystical thinking: *vide* the misinterpretation of Freud's teaching by some disciples who equate his concepts of "Id," "Ego" and "Superego" for the triple oligarchies of gods that were once thought to control man's "psyche," or the misuse of selected

Hellenic myths (Narcissus, Oedipus) not as expressive topical allegories but as supposed "proofs" of man's universal motivations.

Fortunately, this recidivism even in modern psychiatry is far outweighed by recent advances. Thus, in the fields of neurophysiology and psychosomatics psychiatry is re-establishing a scientific liaison with biology and medicine; in the modern developments of psychoanalysis (Fromm-Reichmann, Kubie, French, *et al.*) it has achieved a sounder and more comprehensively dynamic rationale, and in some of its group applications (e.g., mental hygiene, orthopsychiatry; group therapy, etc.) it has become better correlated with anthropology, sociology, political science and such other broad disciplines. Moreover, it has relatively recently begun to derive support from another heuristic source in which it had been conspicuously lacking: namely, validation of its data, hypotheses and methods by laboratory experimentation.

EXPERIMENTAL VERSUS CLINICAL DATA

In all fairness, it must be noted that the clinical psychiatrist might take exception to the validity or relative importance of experimental data. He might insist, for instance, that every human being, in Adolf Meyer's words, is *ipso facto* an "experiment of nature", ready-performed and with results open to inspection. In effect, each person's inborn energies, potentialities and propensities have already been utilized in and influenced by his special familial, educational, social, sexual and other experiences, and in this manner molded into the complex configuration of traits and action-patterns that we call his personality. This in turn is open to retrospective and reconstructive analysis, provided only that our psychologic and psychiatric methods are made sufficiently discerning and penetrating.

Taken at face value, this argument sounds attractive, although one almost immediately wonders why it is not taken as seriously in other fields of medicine in which conclusions derived from clinical histories and observations alone are checked whenever possible by laboratory research. Further appraisal, however, leads to the recognition that *sole* reliance on clinical studies may be especially misleading in psychiatry for many reasons. Three of the most important of these may be outlined as follows.

Complexity and multidimensionality of the data

Human behavior is, perhaps, the most protean and variable of all phenomena. What observer, then,—indeed, what combination of mortals—can possibly catalogue all of its facets, changes and expressions: anatomic, chemical, physiologic, pathologic, motivational, perceptual, conceptual, expressive, social, cultural, and others? And if the totality of behavior can never really be observed, let alone comprehended, in even a single individual, how can we really speak (as so many psychiatrists pretentiously do) of "the person as a whole" while at the same time myopically investigating his conduct by some narrowly constricted technique (e.g. a "psychiatric history," a neurological examination, or a Szondi test) picked on limited and sometimes purely arbitrary assumptions? In short, even though we are given two billion "experiments of nature", we do not necessarily know

what particular phenomena to endow with what special significance for our field of interest.

Limitations of description: But even when we have selected our data, another difficulty arises: how shall we record them? Is any verbal language capable of describing the infinitely variable nuances of human conduct? And are not vaguenesses and confusions multiplied when we attempt to "define" even first-order psychologic abstractions i.e., categories of "motivation", "emotion", "intellect" and so on? What, for instance, are the palpable distinctions among "instincts", "unconditioned reflexes", "id-tendencies", "latent impulses", "goal-directed strivings" and other such postulates as to the basic motivations of conduct? Or, at the level of symbolic evaluation, who is to say whether some pattern of observed conduct arises from "inference", intuition", "prejudice" or "delusion?" In short, we not only do not know what to look for in the welter of human conduct, but our descriptions of artificially isolated phenomena are often inexact, presumptive and judgmental.

Complexity of analysis: Further, our semantic difficulties seem to mushroom incredibly when we attempt to progress from the recording of human behavior to its formulation in generic and causative (etiologic) terms. Here, unfortunately, is where some psychiatrists departed furthest from the rules which govern sound scientific theory: operational definition of terms, parsimony of premise, clarity and coherence of formulation, specificity of application and validation by unprejudiced test. Indeed, until recently it seemed that the wilder or more fantastic the speculation the more it fascinated certain writers in the field. For instance, only two decades ago self-styled "depth metapsychologists" were still promulgating oracular vacuities about "death-instincts", the "racial unconscious", the "birth trauma", "organ inferiority", and so on while their organic-minded psychiatric colleagues were proposing "constitutional inferiority", "stigmata of degeneration", "neurasthenic diatheses", and other sententious but equally baseless etiologic postulates for deviations in behavior they could not understand. All in all, psychiatry (if I, too, may indulge momentarily in the logical sin of animism) even now seems like a child emerging from its private world of uncontrolled fantasy into the less dramatic but more substantial and orderly universe of operational reality.

As has been indicated, however, many influences have stimulated recent progress in the field, not the least of which has been the pressure from psychiatrists themselves for better clinical and experimental validation of psychiatric theses and methods. Indeed, the studies of N. Tinbergen, W. Grey Walter, Horsley Gantt, H. A. Liddell, J. Hunt, David Levy, J. Finesinger, Curt Richter, and many others have indicated that certain basic tenets on which much of modern dynamic psychiatry implicitly rests are demonstrable in nearly all behavior—animal (or even "inanimate") as well as human, and "normal" as well as "abnormal."

Let us, then, proceed to state these tenets—herein called "biodynamic principles"—and in the remainder of this article describe how they are illustrated by typical experiments in animal as well as human behavior.

PRINCIPLES OF BIODYNAMICS

These may be condensed into four relatively simple statements relative to motivation, reaction patterns, substitutive behavior and "neurosis" formation as follows:

Motivation: All behavior is actuated by the current physical needs of the organism in the process of survival, growth and procreation.

Thus, even as the reader peruses this a physiologic want for fluids, or for warmth, or even for relief from bladder tension would, if sufficiently urgent, take precedence over his current interests or more complexly derived "instincts" (e.g., sex or "aggression") considered basic in some systems of psychology.

Reaction Formations: Behavior is adaptive to the "external" environment not in any "realistic" sense, but according to the organism's special interpretations (concepts) of its milieu in terms of its own perceptive-integrative-response capacities ("intelligence") and its unique concatenations of experience.

In the human being these interpretations and reactions become exceedingly elaborate; nevertheless, despite superficial cultural uniformity, each person's concepts of, and reactions to his universe are individually determined. To a literal minded farm laborer, a hammer and sickle are merely the tools of his trade; to a Communist they herald a fanciful Utopia; to an anti-Communist, the same insignium may represent the threat of barbarism and tyranny.

Behavior Substitution: When accustomed methods of achieving a goal are frustrated, behavior becomes deviated into substitutive techniques or orientated toward ancillary goals.

Thus, if a man's methods of wooing a girl meet with rebuff, he tries (a) other methods, (b) another girl or (c) another goal; e.g., achieving success as a religious prophet, a jazz drummer or perhaps as a clinical psychologist.

Neurotic Deviations: When two or more accustomed modes of response become mutually incompatible and conflictual, physiologic tension ("psychosomatic anxiety") becomes manifest and behavior becomes vacillating, inefficient and unadaptive ("neurotic") or excessively substitutive, erratic and regressive ("psychotic").

This principle of inner conflict is expressed or implied by almost every theory of neurosis, albeit the elements supposedly in conflict vary widely in the different contexts: e.g., animal *versus* rational soul (Plato), excitation *vs.* inhibition of conditioned reflexes (Pavlov) or Id *vs.* Ego *vs.* Super-ego (Freud). However, when formulated in biodynamic terms, this theory of conflict is amenable to more direct clinical and, as will be seen, experimental demonstration. There now remains the task of describing as briefly as possible the actual experiments from which the generalized biodynamic principles were derived.

EXPERIMENTS IN BIODYNAMICS

Animal Subjects

Any animal with sufficiently high perceptive-integrative-reactive capacities may be utilized: rat, dog, cat, or monkey. The cat, an animal with easily isolated motivations and relatively high intelligence, was employed in most of the experiments described below.

Motivations: Any relatively strong physiologic want may be evoked: asphyxia, thirst, cold, escape from pressure or pain, erotic excitement, etc.,—all have been tested and employed to motivate specific behavior patterns. However, we have found that hunger for food, though a relatively complex need, is most easily worked with for a number of reasons: it is easily renewable, is satiable in easy stages, and is neither as climactic nor potentially traumatic as are sexuality, cold, pain or other physiologic tensions.

Normal Adaptive Behavior: In a typical experiment, a cat was deprived of food for a day, then placed in a glass-enclosed experimental cage at one end of which was a food box with a hinged lid partially open. The animal, of course, readily learned to secure pellets of food from this box by prying the lid farther open so as to make the food available. The animal was then taught (a) to wait for various combinations of sound and light signals before attempting to feed (conditional responses), (b) to manipulate various electrical switches so as to actuate these signals for itself (manipulative skills) and (c) to close two or more switches a given number of times in definite sequence (space and number categories) or in response to interposed cues (behavioral contingencies). If the training of the animal was too rapid for its age and capacities—and cats seemed to vary in relative intelligence as much as humans—the animal sometimes became recalcitrant, inept and resistive. If, however, the pedagogic process was adjusted to the individual cat, the behavior of the latter continued to be efficient, well-integrated and successful; indeed, pussy—as indicated by her eagerness to enter the laboratory, her avidity (“love”) for the experimenter and the food-switch, and her *legato sostenuto* purring while she worked for her rewards presented the appearance of a “happy” animal, contented in an environment she had sufficiently mastered.

Range of Normal Adaptations: Such control experiments presented an opportunity to investigate whether certain variations in individual and social behavior parallel to those seen in human beings could also be reproduced under laboratory conditions. Some of these studies deserve brief mention.

Habit Idiosyncrasies: If an animal was thoroughly trained to depress a disc-switch to secure food and then the switch was disconnected for several days so that its manipulation produced little or no reward, the animal would develop a marked tendency to push down upon other objects in its environment: saucers, loops, boxes or even other cats. This obsessive manipulative activity took many forms: sitting on the switch or on similar small platforms rather than in more comfortable places, prying into the experimenter’s clothes instead of into the food-box, etc.

Masochism: Even greater deviations in symbol-values and goal-mediation could be produced, including conduct patterns which, when seen in human beings, have been somewhat misleadingly called “self-punitive” or “masochistic.” Thus, a cat was first trained to accept a mild electric shock as a signal for feeding, and then taught to press a switch and administer the shock to itself in order to secure the food reward. The intensity of the shock was then gradually increased to as much as 5000 v. of a pulsating 15 ma. condenser discharge, yet the animal continued to work the switch avidly for the food. The food reward was then given

only rarely or even discontinued for long periods; nevertheless, in the interim the animal persisted in its accustomed patterns of depressing the switch, apparently solely for the substitutive experience of a "painful" electric shock. Such observations suggest that, contrary to the biologically paradoxical postulate of a death-instinct, "masochistic" behavior is not basically "self-punitive" or destructive, but rather a seeking for survival by patterns of evaluation and response that seem awry only to an observer unacquainted with the special experiences of the subject. Clinically, we can understand why a woman may enjoy only certain "painful" forms of sexual intercourse when we learn that she reached her first orgasm while being beaten or raped, and that thereafter she valued all aspects of the erotic associations including those considered by others as "painful." Similarly, we can cease to wonder why a man marries a succession of shrewish wives if we determine under deeper analysis that what appears to his friends to be their nagging and persecution simply represents to him the security he had once experienced with his tyrannical but devoted mother.

Social Dominance or Submission: "Social" interactions can also appear in animal groups with revealing clarity. Thus, if after a given signal two cats compete for a single food-reward they may, at first, scuffle a bit at the food box. Soon, however, all external evidences of competition abate and only one of the animals—usually the more alert and intelligent—responds to the signal while its partner, though hungry, waits patiently until the "dominant" animal is either satiated or removed from the cage. Stable hierarchies of "privilege" can be produced in groups of four or more animals, although in the same group the animals may range themselves in a different order with regard to precedence in playing with parts of the apparatus or chasing a mechanical mouse. In short, a stratified "society" with fixed rankings in various activities evolved under the conditions described.

One variant of these experiments was particularly enlightening, since it seemed to reproduce in cats paradigms of "worker-parasite relationships" usually seen only in more elaborate forms of social organization. In these experiments two cats, each of which had been trained to manipulate a switch to secure food, were placed in the cage together. This time, however, a partition was so arranged that the animal which essayed to work the switch was delayed in returning to the food-box for its reward until its less enterprising partner had eaten the pellet. Under these circumstances some pairs of cats evolved a form of co-operative effort in which, for a day or so, they alternately worked the switch to feed each other. This co-operation, however, lasted no longer among cats than it does among men: one animal sooner or later showed tendencies toward "parasitism" in that it ate the pellets produced by its partner's efforts but refused to leave the food to manipulate the switch. The worker animal, finding its own "co-operative" behavior completely unrewarding, in turn ceased to produce food, so that both animals, the parasite usually near the food-box and the worker near the switch, lolled about the cage for hours or days in a travesty of a sit-down strike. But as hunger increased—generally most urgently in the relatively undernourished worker—the latter, in attempting to break the impasse, would discover that if the switch

were depressed 6 or 8 times in rapid succession so that as many pellets were deposited into the food box, he could traverse the barrier and get the last one or two before the parasitic partner had time to gulp them all. In most experiments the end result was that the "worker" animal labored hard and eagerly for a meager living while supporting its parasitic partner in leisure—a form of relationship apparently accepted by both animals. However, two workers out of some 14 studied solved the situation with a flash of technological genius not anticipated by the experimenter: viz., they learned to wedge the switch into a recess in the cage so that, with its electrical circuit closed and the mechanical feeder operating continuously, both animals could feed without further effort by either.

Social Aggression: It may have been noted in the experiments described thus far that each animal pursued its own goals with its own initiative and techniques, without necessarily becoming hostile or combative toward others even in circumstances of direct rivalry. Indeed, so infrequently did overtly aggressive behavior occur that special experiments had to be devised to determine the specific circumstances under which such behavior could be elicited. In general, these studies demonstrated that animals became overtly belligerent under two sets of conditions: (a) when they were displaced from a position of social dominance to which they had become thoroughly accustomed or (b) when their goal-seeking activities were internally inhibited by neurotic conflicts. The first of these contingencies may be illustrated in a typical series of experiments as follows:

Let four cats compete for food under controlled conditions in Group A until Cat A1 emerges dominant, with A2, A3 and A4 in the hierarchy of precedence below him. Let Cats B1, B2, B3, and B4 range themselves correspondingly in Group B. If A1 is now paired with B4 the latter, accustomed to permit all other animals to feed before him, will offer no competition and the new pair remains peaceful. The same interactions of course occur when B1 is paired with A4. But if A1 and B1 are paired after each had been accustomed for weeks or months to dominance in its respective group, a new contest of speed and skill in securing the food on signal occurs. As before, each animal at first strives for the reward directly and deviates none of his energies into physical attacks on the other. Once again, of course, one animal emerges dominant—say B1—and thenceforward secures the food pellet after each signal. A1 now gives up his own efforts to obtain the food reward as long as B1 is in the cage. Instead, between signals A1 may sit on the food-box menacing B1 with tooth and claw or may even attack him viciously, yet at no time does A1 utilize such physical attacks as a means of securing the food-pellet himself. Other pairings (A2-B3, B2-A3, etc.) evoke less definitive reactions ranging modally between the extremes of peace or hostility here described.

As indicated previously, aggressivity also appears when a well-patterned goal-directed striving in an animal is strongly inhibited by an adverse experience. For instance, if in Group B the dominant animal is made fearful of feeding on signal he will abandon this learned response and permit the sub-dominant B2 to feed instead—yet attack the latter animal between feedings. The induction of such "neurotic" deviations of energy will be more fully described below; however, it

may be emphasized here that hostility and aggression appeared in our experiments only under conditions of external frustration or internal inhibition. These biodynamic observations therefore support the clinical and sociologic conclusions of Dollard, Horney, the author and others that hostilities among human beings also spring from the frustrations of their unconquered environment and the anxiety-ridden inhibitions imposed by their persistently barbarian culture—and not, as some would have it, from an inborn homo-suicidal “death instinct.” Nor, as the author recently pointed out in an article on the social implications of biodynamics, is this point purely of academic interest. If aggression is merely a blindly exaggerated reaction-formation to perceived or conceived threat, then the hope of humanity lies in the abolition of tragic want and raging despair. If, however, aggression is the inevitable expression of a primeval and implacable “instinct” of destruction then we must indeed resign ourselves to the impending self-destruction of mankind. But in the latter case, why bother to think, write, or treat in the face of the holocaust?

THE PRODUCTION OF EXPERIMENTAL NEUROSES*

Perhaps the portion of our work most relevant to clinical psychiatry (in its older definition as a study not of the totality, but of the “abnormalities” of behavior) has been concerned with (a) the production of experimental neuroses in animals and (b) a study of the methods for restoring the behavior of such animals to “normal”. This section of the present report must of necessity be even more greatly condensed than the preceding, but possibly the following brief description of the rationale, techniques and results of the experiments will indicate their main significance.

Rationale: As previously indicated, many theories as to the causes of neurotic aberrations converge on the concept of “conflict”, whether this conflict is conceived to be between disparate “humors of the body” (Galen), “inhibition *vs.* excitation” (Gantt), “love against hate” (Karl Menninger) or other such noumena. In biodynamics this field theory is somewhat clarified by defining the conflict as occurring between or among patterns of behavior rendered mutually exclusive because (a) they arise from incompatible needs, or (b) they cannot co-exist in space and time. This general statement can be exemplified by a relatively simple method of producing an experimental neurosis in animals.

Technique: A cat was trained to manipulate an electric device which, in the order named, flashed a light, rang a bell and deposited a pellet of breaded salmon in a food-box. The animal was permitted over a period of months to become thoroughly accustomed to this routine of working for the food. One day, however, just as the animal was about to consume its reward for honest labor it was subjected to a physically harmless but “psychically traumatic” stimulus, e.g., a mild air-blast across its snout or a pulsating condenser shock through its paws. The animal, of course, dropped the food, beat a startled retreat from the food-box and began to show hesitation and indecision about again manipulating the

* Grateful acknowledgement is made to the U.S. Public Health Service for grants-in-aid that made these research studies possible.

switch or approaching the box. When it did so, it was permitted to feed several times but then subjected once more to the disruptive blast or shock. After from two to seven repetitions in as many days of such conflict-inducing "neurotogenic" experiences, the animal began to develop aberrant patterns of conduct so markedly like those in human neuroses that the two may be described in the same terms. Examples are the following:

Physiologic Anxiety: This was manifested by a rapid heart, full pulse, catchy breathing, raised blood pressure, sweating, trembling, erection of hair and other evidences of pervasive physiologic tension.

Hypersensitivities and Phobias: The animal showed extreme startle reactions to minor stimuli, and became "irrationally" fearful not only of physically harmless light or sound stimuli, but also of closed spaces, air currents, vibrations, food pellets (or all food), caged mice and many other stimuli directly or remotely associated with its conflictful experiences. Odors welcomed in the normal state became particularly disturbing to the neurotic animal until, in further control observations, they were neutralized by a chlorophyll-containing deodorant placed in the apparatus.†

Psychosomatic Dysfunctions: Neurotic animals developed gastro-intestinal disorders, recurrent asthma, persistent salivation or diuresis, sexual impotence, epileptiform seizures or muscular rigidities resembling those in human hysteria or catatonia.

Motor Changes: Peculiar stereotypes of behavior ("compulsions") emerged, such as restless, elliptical pacing or repetitive gestures and mannerisms. One neurotic dog could never approach his food until he had circled it three times to the left and bowed his head before it.

Social Alterations: Neurotic animals lost their group dominance and, as indicated, became reactively aggressive under frustration. In other relationships they regressed to excessive dependence or various forms of kittenish helplessness.

Experiments with Monkeys

It may be added here that in more recent experiments with various species of monkeys not only has it been possible to establish and study highly complex response patterns (for example, "reading" behavior, time-perception, etc.) but also to use completely "symbolic" traumata (e.g., the exhibition of a toy rubber snake when food was anticipated) as means of precipitating an experimental neurosis. As might be expected, the neurotic behavior of the monkey was then even more closely similar to that of the human in a variety of ways. Psychosomatically, individual monkeys developed asthma, functional colitis, ties, "hysterical" paralyses and other organic or neuromuscular disturbances; sexually, homoeroticism or persistent masturbation and autofellatio was substituted for previously normal heterosexual conduct; whereas socially, complex dominance relationships, defensive "friendships", or generalized aggressions occurred in patterns quite parallel to those observable in groups of neurotic or psychotic children and human adults.

† The studies of normal and neurotic olfactory behavior were supported by a special grants-in aid from the Airkem Corporation.

EXPERIMENTAL PSYCHOTHERAPY

In nearly every case the neurotic patterns described above rapidly permeated the entire life of the animal and persisted indefinitely unless "treated" by special procedures. These, too, were worked out in experiments too numerous and varied to be recounted here in detail; however, the techniques found to be most effective experimentally were so significantly similar to those used in the treatment of human neuroses that again the two may be outlined in parallel order. As nearly as they could be isolated, the methods were as follows:

Change of Milieu: A neurotic animal given a prolonged rest (three to twelve months) in a favorable home environment nearly always showed a diminution in anxiety, tension, and in phobic-compulsive and regressive behavior. However, these neurotic patterns were prone to reappear when the animal was returned to the laboratory even though it was not subjected to a direct repetition of the conflictual experiences. To draw a human analogy, a soldier with severe "combat neurosis" may appear "recovered" after a restful sojourn in a base hospital, but unless his unconscious attitudes are altered his reactions to latent anxiety recur cumulatively when he is returned to the locale of his adaptive conflicts.

Satiation of a Conflictful Need: If a neurotically self-starved animal which had refused food for two days was forcibly tube-fed so that its hunger was mitigated, its neurotic manifestations correspondingly decreased. Hippocrates is reported by Soranus (perhaps apocryphally) to have utilized a parallel method in human psychotherapy. Hippocrates, it seems, was called into consultation to treat a strange convulsive malady which was keeping a recent bride virginal. Discerning, after a private interview, that she was torn between strong sexual desires neatly balanced by fear of injury, Hippocrates advised the husband "to light the torch of Hymen" with or without the patient's consent. The results of the therapy are not recorded, but Soranus parenthetically comments that, in general, it is only of temporary advantage "to substitute one Fury for another."

Forced Solution: A hungry neurotic cat was prevented from escaping from the apparatus and instead was brought mechanically closer and closer to the feeder until its head was almost in contact with a profusion of delectable pellets. Under such circumstances some animals, despite their fears, suddenly lunge for the food; thereafter, they need lesser degrees of mechanical "persuasion" until their feeding-inhibition disappears altogether carrying other neurotic generalizations with it. This method is a variation of the Hippocratic one mentioned above, but entails a greater degree of activity on the part of the patient. In some ways, the "therapy" is akin to pushing a boy afraid of water into a shallow pool. Depending on his capacities for reintegrating his experiences (in analytic terms, his "Ego strength"), he may find that there was, after all, no reason for fear—or he may go into a state of abject terror and thereafter hate not only water, but pools, swimming—and all future therapists. Because of the latter eventuality ruthless force is generally considered a dangerous method in dealing with neurotic anxieties.

Example of Normal Behavior: An inhibited, phobic animal paired for several weeks with one who responds normally in the experimental situation will show some diminution in its neurotic patterns, although never to the degree of complete "recovery." In like manner problem children do better when they have an oppor-

tunity to live with normal youngsters in an environment that favors normality—although more specific individual therapy is nearly always necessary to complete the “cure.”

Re-education by a Trusted Mentor: As noted, a neurotic animal, perhaps by the very virtue of its regression to earlier patterns of relationship, becomes exceedingly dependent upon the experimenter for protection and care. If this trust is not violated the latter may then retrain the animal by gentle steps: first, to take food from his hand, next to accept food in the apparatus; then to open the box while the experimenter merely hovers protectively, and finally to work the switch and feed as formerly without further “support” from the therapists. During its “rehabilitation” the animal not only re-explores and resolves its hunger-fear conflicts but also masters and dissipates the symbolic generalizations that spring from this nuclear “complex”: i.e., its inhibitions, phobias, compulsions and other neurotic reactions. This, indeed, may be the paradigm for the basic processes in much clinical psychotherapy. The neurotic patient channelizes his needs for help toward a therapist upon whom he transfers his dependence and other relationships. The therapist then utilizes this “transference” with optimal patience and wisdom to guide and support the patient as the latter re-examines his conflictful desires and fears, recognizes his previous misinterpretations of reality and essays new ways of living until he is sufficiently successful and confident to proceed on his own. Whether this be called re-education, re-training, re-habilitation or psychoanalysis depends more on the context of the problem, the necessity for thoroughness in anamnestic review and symbolic analysis and the form of utilization of the interpersonal relationships involved than on any fundamental differences in the essential dynamics of the respective procedures.

Physio-pharmacologic Methods: As the experiments described thus far have indicated, many of the vectorial processes of so-called functional psychotherapy can be isolated in principle and demonstrated in operation. There remains, however, the fact that various physical methods such as the use of drugs, electroshock, etc., have also proved clinically useful in the treatment of behavior disorders. Space now remains only for the most cursory review of specific further experiments dealing with this subject.

Action of Various Drugs: Preliminary tests of the effects of various sedative and narcotic drugs on normal animals showed that, in general, such drugs disorganized complex behavior patterns while leaving relatively simple ones intact. Thus, in one series of experiments an animal was taught in successive stages (1) to open a food box, (2) to respond to food-signals, including signs reading FOOD or NO FOOD, (3) to operate the signal-switch, (4) to work two switches in a given order, and finally (5) to traverse a difficult maze to reach one of the switches. If the animal was then drugged with a small dose of barbitol, morphine or alcohol, it would become incapable of solving the maze but would still work the food-switches properly; with larger doses, it could “remember” how to work only one switch; with still larger doses, earlier stages of learning would also be disintegrated until finally it lost even the simple skill required to open the food-box. Conversely, as the animal recovered from its intoxication its learned responses

were reconstituted in their original order. If now the animal was made neurotic by an adaptational conflict it developed a new set of highly intricate and elaborate reactions: i.e., inhibitions, phobias, compulsions, etc., as previously described. *These, too, proved relatively more vulnerable to disintegration by the sedative drugs than the simpler, pre-neurotic behavior patterns*, so that if a neurotic animal was given barbitol or morphine its anxiety reactions and inhibitions were significantly relieved. In effect, instead of crouching tense and immobile in a far corner or showing panic at the feeding signals, it could respond to the latter by opening the box and feeding (in a somewhat groggy but comparatively effective manner) as though, for the time being, its doubts and fears were wraiths forgotten.

Drug Addiction: In one variant of these studies in which alcohol was used as the nepenthic drug the animals which experienced relief from neurotic tensions while partly intoxicated were later given an opportunity to choose between alcoholic and non-alcoholic drinks. To our surprise (and, it must be confessed, subdued delight) about half the neurotic animals in these experiments began to develop a quite unfeline preference for alcohol; moreover in most cases the preference was sufficiently insistent and prolonged to warrant the term "addiction". In further proof of its neurotic basis the induced dipsomania generally lasted until the animal's underlying neurosis was relieved by the dynamic methods of therapy described above. It seems redundant to discuss the human analogues to these experimental observations.

Tension-relieving Effects: In still another series of experiments we observed that the administration of hypnotic drugs (including alcohol) so dulled the perceptive and mnemonic capacities of animals that they were, while thus inebriated, relatively immune to the neurosis-producing effects of traumatic experiences. In this connection it may be recalled that many a human being long ere this has been tempted, through subversive experience, to take a "bracer" before bearding the boss, getting married, flying a combat mission or facing other presumed dangers.

Effects of Cerebral Electroshock: In view of the widely broadcast and as yet scientifically questionable claims made for the efficacy of various forms of "shock therapy" for all forms of behavior disorders, we also investigated the effects of cerebral electroshock on our neurotic animals. In briefest summary, we found that when the ordinary 60-cycle current usually employed clinically was passed through the brain of the animal, the resultant shock acted like an intoxicant drug to disintegrate complex and recently acquired patterns of behavior, whether these were "normal" or "neurotic". Unlike most drugs, however, electroshock produced *permanent* impairment, however subtle, of future behavioral efficiency, even though this could not be correlated with pathological changes in the brain detectable by present methods. Weaker or modified currents now being tested clinically (i.e., the direct square-wave Ledue type) produced lesser degrees of deterioration in our animals, but also had less effect on their neurotic behavior. All in all, these experiments supported the growing conviction among psychiatrists that electroshock and other drastic therapies may be useful in certain relatively recent and acute psychoses, but that the cerebral damage they produce makes their indiscriminate use replete with potential tragedy. More recent ex-

periments in our laboratory indicate that this is probably true also for the operations of lobotomy, lobectomy and thalamotomy.

SIGNIFICANCE OF THE WORK

This, then, is a summary—possibly condensed beyond the limits of lucidity—of a long series of experiments designed to analyze the biodynamics of behavior and to discern principles that would apply alike to “normal” and “abnormal” conduct, to animal and human subjects, and to experimental and clinical therapy. The gap between the responses of cats, dogs or monkeys in cages and the conduct of man in society is undeniably wide; certainly man, of all creatures, has developed the greatest facility in experiential association and integration, the highest capacity for symbolic, verbal and other imagery, and the most elaborate repertoire of “normal”, “neurotic” and “psychotic” behavior patterns in a constantly changing social and cultural milieu. And yet, as elsewhere in medicine, the best way to unravel an especially complex problem is to take it into the laboratory as well as the clinic, investigate it by specially designed experiments, check their results with a rigid self-discipline that eliminates subtle errors and cherished preconceptions, and so advance bit by bit toward clearer formulations of general principles and more pertinent applications of them. In psychiatry, such experimental and operational approaches, when correlated with clinical practice, may not only dissolve the verbal barriers among the various schools and methods but may also foster a needed rapprochement between psychiatry on one hand and scientific medicine and the humanities on the other.

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THE EXTRACELLULAR COMPARTMENT: A COMPARISON OF THE CHLORIDE AND INULIN SPACES*

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It has been customary to regard the fluids of the body as divided into two distinct compartments, one extracellular, the other intracellular. According to this view, the extracellular compartment is comprised of the plasma and the interstitial fluid, the latter a homogeneous solution with the chemical composition of plasma ultrafiltrate. The intracellular compartment consists of fluid located within the boundaries of protoplasm and contains electrolytes maintained at widely different ionic concentrations from that in the plasma ultrafiltrate. However oversimplified and inadequate this concept may be, it has served as a frame of reference from which valuable information has been derived. Although significant refinements have been achieved in the measurement of ionic concentrations, the volume of the extracellular compartment has defied direct quantitative measurement.

Based on the assumption that chloride has a homogeneous and exclusively extracellular distribution, the chloride space has served as an index of the volume of the extracellular compartment. Thiocyanate and other foreign substances which are alleged to occupy a comparable volume have on the strength of this correspondence also enjoyed popularity as measures of the extracellular compartment. Recently, inulin and several other large molecules have been found to occupy a volume 20 to 30 per cent smaller than the classical chloride space. This latter smaller volume has been interpreted by some as the true extracellular space. Since it is unlikely that a homogeneous fluid compartment be freely permeated to a consistently different extent by two classes of substances, the discrepancy between these two volumes has precipitated considerable but as yet inconclusive debate.

A critical review of the evidence supporting both of these spaces as indices of the extracellular compartment and a consideration of implications arising from the differences in their volumes may be pertinent.

THE "CHLORIDE" SPACE

The assumption that chloride is evenly distributed and entirely confined within the extracellular compartment provided the basis for its use as an index of the extracellular fluid volume. Though never actually proved, this assumption and the data derived from it have seemed reasonable to many investigators (1-5). Three arguments are often cited to support the concept that chloride is limited to the extracellular compartment: 1) The chloride space of muscle corresponds to the tissue space of muscle as measured histologically;

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2) the chloride of muscle is freely diffusible and is in rapid ionic exchange with plasma chloride; and 3) the chloride space allegedly corresponds to the thio-cyanate, sulfate, sucrose and mannitol spaces.

Fenn, Cobb and Marsh (6), studying the electrolyte content of frog muscle, noted that if all the chloride were confined to 14.7 per cent of the tissue, its concentration would be the same as that of a plasma ultrafiltrate. Since histological studies have indicated that the volume of tissue spaces in muscle ranges from 14.5 per cent to 17.5 per cent (7), the correspondence between this volume and that required to produce isotonicity of the chloride ion suggested to these workers that all the chloride was extracellular. Assuming that the water content of muscle cells and red cells is identical, and that all muscle solids are intracellular, Peters calculated from the known water content of human muscle (8) that the volume of the interstitial fluid is 18.6 per cent (1). This gross correspondence between various estimates of the extracellular fluid volume merely demonstrates that chloride in muscle is predominately extracellular but does not argue that it is exclusively so. As much as $\frac{1}{5}$ to $\frac{1}{6}$ of the total muscle chloride could be separated from the ultrafiltrate fluid phase, either by intracellular disposition or by association with the underlying intercellular matrix, without being detected by such crude correlations. On the basis of similar reasoning applied to comparable approximations, it was concluded that sodium, too, was limited to extracellular distribution in muscle (1, 9). However, if this were true, the high sodium/chloride ratio in muscle as compared to a simultaneous ultrafiltrate of plasma would be difficult to explain (2). Furthermore, the penetration of muscle cells by sodium after potassium depletion (10) and the reciprocal relation of intracellular sodium and potassium in adrenal hormone therapy (11), experimental hypertension (12-14), alkalosis (15-17), recovery from acidosis (18), vomiting (19, 20), Cushing's syndrome (21), and the post-operative state (22) have proved that sodium is subject to variable intracellular disposition.

That the chloride of muscle is rapidly and freely diffusible was suggested by Fenn, Cobb and Marsh (6), who demonstrated that muscle tissue immersed in isotonic glucose rapidly loses all of its chloride. Furthermore, the chloride content of muscle tissue suspended in any solution is directly proportional to the concentration of chloride in the solution used (6, 23). Amberson *et al.* (24) were able to remove virtually all of the chloride of muscle by the *in vivo* replacement of chloride with sulfate. However, that an ion is in rapid exchange with the plasma and that its tissue concentration reflects primary changes in plasma concentration does not in itself prove exclusive extracellular distribution of this ion. Potassium, for example, satisfies in part both these prerequisites despite its preponderant intracellular disposition (10, 25).

Furthermore, several observations have revealed that even in muscle a significant proportion of chloride is not in rapid equilibrium with the bulk of extracellular chloride. In contrast with Amberson's and Fenn's observations, Yannet and Darrow (26) noted that although there is a linear relation between muscle chloride and serum chloride concentrations, a significant amount of chloride remains in the tissues when the serum chloride concentration is extrapolated

to zero. This amount, consisting of one meq./100 gms. of dry muscle, represents about 15 per cent of the chloride normally present in muscle. Also suggestive of fixed chloride in muscle is the demonstration by Manery and Haege (27) that the 52 minute Cl^{35} space, the rapidly miscible chloride, is about 18 per cent lower than the total chloride space in muscle. That the excess fixed chloride in muscle reflects in part its connective tissue content is indicated by the reduction in muscle chloride content which is noted following careful removal of fascia and connective tissue (28). Manery and Haege (27) have shown, however, that unlike muscle chloride, connective tissue (tendon) chloride equilibrates rapidly and completely with radio chloride. This suggests that at least some of the fixed chloride of muscle is neither in the interstitial fluid nor in the connective tissue but is possibly within the cells themselves.

That the chloride space is similar to the volume of distribution of sodium thiocyanate, (29-34) and ostensibly of sulphate, sucrose (31) and mannitol (36), is often cited as evidence that these substances measure a finite compartment. For the most part these similarities are based on the comparison of average spaces rather than on the simultaneous measurement of these various volumes in the same subject. This weakens the value of this correspondence considerably since there is a large spread in determinations noted from individual to individual and even at different times in the same subject. Furthermore, thiocyanate does not fulfill the basic requirements of cellular impermeability. It penetrates erythrocytes, gastric musosa and other tissues (29, 31, 36). Under the most favorable circumstances it measures a volume variably intermediate between the total body water and the extracellular volume. In certain pathological states such as malaria and other fevers (37-39) the rate of cellular penetration becomes so rapid that even within four hours the volume of distribution of thiocyanate approaches the value for total body water. In addition, a variable proportion of the thiocyanate is bound to serum protein (31, 40) adding another unpredictable factor in calculating the space. Crandall and Anderson, (29) who developed the method, emphasized that thiocyanate provided only an index for the estimation of "available water" and hoped that it would provide a method only for detecting gross changes in the extracellular volume.

The 1-2 hour sulphate space includes a significant proportion of cellular water (41). Spaces determined with sulphate, sucrose and mannitol by a single injection technique may be invalidated by the rapid urinary excretion of these molecules which precludes the establishment of equilibrium distribution (31). Furthermore, sucrose is metabolized in some species (42) and mannitol is metabolized in all (43). Each of these circumstances renders the respective volumes of distribution artificially high, unless corrections are made. The correspondence of these uncorrected spaces with the chloride space does not convincingly enhance the argument that chloride is exclusively extracellular.

In tissues other than muscle, the presence of chloride outside the fluid phase of the extracellular compartment is no longer questioned. Gastric and pyloric mucosa, connective tissue, skin, testes, red blood cells and liver all contain excessive quantities of chloride as reflected by their high chloride/sodium ratios com-

pared to simultaneous plasma ultrafiltrate ratios (28, 44). Amberson *et al.* (24) have demonstrated that considerable quantities of this excess chloride is not directly responsive to changes in plasma chloride concentration.

Measurements of total chloride space in animals either by direct chemical analysis (3), the *in vivo* dilution of bromide (which is distributed identically with chloride) (46), or chloride³⁶ (47) have revealed total chloride spaces of 25 to 40 per cent. These values are significantly higher than the most generous estimates of the extracellular fluid volume.

Despite the convincing evidence that a significant proportion of the total body chloride is confined outside of the extracellular fluid phase, some have argued that the proportion of non-extracellular chloride is generally consistent, particularly in muscle tissue. Consequently it has been contended that balance studies and muscle analyses using chloride as a reference ion, even under abnormal circumstances, will reveal relative changes in the extracellular fluid volume. Recently however, considerable evidence has accumulated to suggest that the proportion of chloride contained outside of the fluid phase of the extracellular compartment may undergo significant variation.

Swingle *et al.* (48) 15 years ago demonstrated that in the fasting adrenalectomized dog, the administration of adrenal cortical extract produced signs of plasma volume expansion without detectable changes in serum electrolyte concentrations. Swingle concluded that the adrenal gland conditions the distribution of water and electrolytes in the body and that adrenal activity may effect the transfer of osmotically active particles of sodium and chloride from the tissues to the interstitial fluid, a concept which has been amply confirmed now by others (50-53). That such a change could be accounted for by an inexplicable shift of interstitial fluid into the capillaries, as suggested by others (49), is in direct violation of Starling's fundamental hypothesis. Crismon, *et al.* (54) demonstrated that potassium loading in animals induced a transfer of chloride into cells. Boyle and Conway (55) and Wilde (56) also have demonstrated a shift of chloride into muscle cells following progressive elevation of the extracellular potassium concentration. Recently Elkinton *et al.* (17) have pointed out (9) that the use of chloride as an index of the extracellular fluid volume often leads to absurd results in interpreting balance data obtained in metabolic alkalosis and acidosis.

In contrast to earlier concepts, it is now realized that the fluid which composes the extracellular compartment is neither anatomically or biochemically homogeneous (57, 58). In addition to the free interstitial fluid which represents an ultrafiltrate of plasma, there is fluid which, though excluded from cells, is nevertheless contained within such structural elements as connective tissue and bone. Furthermore, this solid phase fluid has a biochemically different composition from that in a plasma ultrafiltrate, there being an excess of chloride in connective tissue and an excess of sodium in bone (29). Also anatomically extracellular is the fluid contained in serous cavities, gastro-intestinal tract, the biliary system, the lumina of secretory glands, the eyes and cerebrospinal spaces. Finally, to add to the complexity of a subdivided extracellular compartment, chloride ion is

also located intracellularly in specific cellular groups (24), possibly to some extent in all. Any measurement of the over-all chloride space therefore includes a heterogeneous collection of varied fluid and solid phases which cannot represent one anatomical or physiological homogeneous extracellular phase. The use of chloride as an index of the extracellular volume in normal muscle tissue is valid, provided a 15 to 20 per cent correction is made for the proportion of fixed or confined chloride (26). However, even in muscle tissue, its use as a measure of the extracellular volume under abnormal physiological circumstances may be subject to error.

THE "INULIN" SPACE

Because of the inadequacies of the chloride space, a substance was sought which would be excluded from cells but which would nevertheless be distributed homogeneously throughout the extracellular fluid compartment. As previously pointed out (29), such a substance ideally should also fulfill the following conditions: 1) fairly rapid and uniform distribution, 2) no formation or destruction in the organism, 3) negligible osmotic effect, 4) slow or measurable elimination from the body, 5) no toxicity, and 6) accurate and easy measurement.

When a constant infusion technique is used to circumvent rapid urinary excretion, inulin has proved to be a suitable reference substance for measurement of the extracellular fluid volume (59-62). It is not metabolized to any appreciable degree in the few hours that it remains in the body (63, 64). It is not an electrolyte, is lipid insoluble, has a large molecular weight (ca 5101) (65), has an elongate structure, and does not dissociate appreciably in solution (66); all circumstances which reduce the probability of cellular penetration. It does not penetrate the erythrocyte (64), the bile (67), or the gastric juice (68), nor does it escape through the normal renal tubules (64). The rapid and virtually complete recovery in the urine, now confirmed by numerous observers (59, 61, 69-71) in itself argues strongly against metabolism, cellular penetration, or significant extra-urinary excretion. Furthermore, it is physiologically inert, completely non-toxic, and exerts negligible osmotic pressure (63, 72).

The volume of distribution of inulin has been shown to average 16 per cent of body weight in normal adult man with a range of 11 to 20 per cent (62). This wide range reflects inversely the variable fat content of the body. The inulin space averages 25 per cent in infants (73), 19 per cent in dogs (60), 18 per cent in monkeys (74), and 25 per cent in rabbits (75). The length of infusion necessary to provide maximum volume of distribution of inulin (equilibrium distribution) varies from species to species, ranging from 2 hours in the dog to 4-6 hours in man. In normal subjects, once equilibrium distribution has been attained, a 4-5 fold prolongation of the infusion time does not significantly expand the over-all inulin space.

Using the constant infusion technique, the volumes of distribution of sucrose, ferrocyanide and inulin agree within the limits of experimental error (76, 71). The identity of ferrocyanide and inulin spaces has been established by simultaneous determinations of the two in a single subject (71), that of sucrose and

inulin in repeated studies in the same subject on successive days (76). If correction is made for metabolism, the mannitol space also agrees with the inulin space in the same subject (43, 77). The correspondence of these four spaces and their reproducibility from day to day argue that they measure a finite proportion of fluid in the body. Radiosulphate distributes itself, within 18 minutes, in a space corresponding to about 16 per cent of body weight in man, and thereafter the volume of distribution gradually expands (41). Thiosulphate, by a method employing back extrapolation, is also apparently distributed in 16 per cent of the body weight (78). However, since methods for calculating spaces from the rapidly falling plasma levels of an injected substance are subject to considerable error, and since thiosulphate has not been checked directly against inulin in the same subject, this correspondence of the thiosulphate and inulin spaces may be fortuitous.

Though these molecules all apparently measure the same space, we have preferred to continue using inulin since 1) the calculation is direct and does not require back extrapolation or corrections for metabolism, 2) simultaneous determinations can be made of the glomerular filtration rate, and 3) its large size makes it unlikely that any detected expansions of the space are due to cellular penetration of the injected molecule.

The main disadvantage of inulin is the length of infusion (4-6 hours) necessary to assure equilibrium distribution. In the presence of gross edema or anasarca, this infusion may have to be prolonged to 36 hours or longer, making the inulin method impractical under such circumstances (79). A more rapidly diffusing molecule such as sucrose or ferrocyanide may be more useful in such studies although even with these smaller molecules considerable prolongation of the infusion will be necessary.

In addition to the technical difficulties of maintaining a steady 36 hour infusion, any circumstance where inulin remains in contact with body tissues for prolonged periods of time may lead to certain errors not encountered in the usual experiment. Cotlove (80) has noted that the prolongation of an inulin infusion from 2 to 15 hours in a rat increased the ratio of the inulin/chloride space in muscle from 0.82 to 0.92. The significance of this finding is unknown, but it has been interpreted as indicating a slow rate of diffusion of the inulin molecule to recesses of the extracellular compartment which are far distant from the capillaries. This seems unlikely, however, in such a vascular tissue as muscle, especially since exercise which should increase the speed of physical mixing did not seem to effect this rate. Other possible explanations also exist. It has been pointed out that the recovery of inulin in man is virtually 100% in the usual experiment in which all the inulin is recovered within 24 hours. On the basis of studies in temporarily anuric patients in whom injected inulin remained for several days, Finkenstaedt *et al.* (81) have reported that recoveries are not complete. It may be that 15 hours in a rat with its higher metabolic rate is analogous to several days in the human, and that if inulin is allowed to remain in contact with the body tissue for this period of time, a significant amount of metabolic breakdown, cellular penetration or extrarenal excretion will become evident.

In the usual experiment in man, such is not the case, and prolongation of the infusion even from 6 to 24 hours does not expand the volume of distribution of inulin (61). In any study, however, where inulin is not completely recoverable in the urine the possibility that some has been lost by metabolic breakdown or extrarenal excretion will render the results suspect.

Because of its anatomical barriers, it should not be surprising that the solid phases of the extracellular compartment contained in bone and tendon are hardly accessible to the inulin molecule. Even radiosodium equilibrates with less than 50 per cent of the sodium of bone in 24 hours (82). Kruhoffer (67) has demonstrated with crude tissue techniques that inulin penetrates only 50 per cent of the water of tendon. The nature of the water which is not accessible to inulin, whether free or perhaps associated in some way with the excess chloride in the solid phase of tendon, is as yet unknown.

It was made apparent in the discussion of the chloride space that this ion was distributed in a volume variably larger than the true extracellular space. From the foregoing discussion, it is also apparent that by virtue of its relative exclusion from the solid phase portions of the extracellular compartment, the inulin space is somewhat smaller than the total extracellular compartment. However, the correspondence of inulin, sucrose, ferrocyanide and mannitol spaces suggest that these molecules measure a finite and reproducible fluid volume. Analyses of muscle in man (79), rat (80), and frog (83) indicate that the measureable inulin and sucrose space approximates 82 per cent of the chloride space in muscle. This figure corresponds with the observations of Manery and Haege (27) who noted that only 82 per cent of muscle chloride exchanges rapidly with radiochloride. It also agrees with Yannet and Darrow's finding (26) that about 15 per cent of muscle chloride was fixed and did not reflect changes in plasma chloride concentrations. This correspondence of figures suggests that the inulin space delineates that fluid phase of the extracellular compartment which has the chemical composition of an ultrafiltrate of plasma and which is in free and rapid exchange with the circulation.

Since the discrepancy between the chloride and inulin space is due to an actual difference in their distribution within the body, it should not be surprising that marked changes can occur in either space without comparable changes occurring in the other. The use of chloride as an index precludes by definition the detection of any endogenous shift of chloride containing fluid into or out of the ultrafiltrate fluid phase of the extracellular compartment. That such shifts do occur was first indicated indirectly by the studies of Swingle (48) which was mentioned in an early part of this review. Assuming that inulin is an index of this fluid phase, it has been possible to demonstrate directly such endogenous shifts of salt containing fluid. It has been found, for example, that DOCA, cortisone and ACTH may evoke an isotonic expansion of the fluid phase of the extracellular compartment in the absence of a positive exogenous balance of salt (51-53). Indeed, it appears reasonable that these hormonal agents which are known to effect expansions of the extracellular volume by their salt retaining influences on the body should also augment the extracellular

fluid phase by endogenous redistribution of sodium and chloride from other phases. Adrenalectomy, on the other hand, evoked dehydration by both its renal and extrarenal effects (50, 51). Using these methods, acute reduction in plasma volume and dehydration also have been shown to induce an endogenous redistribution of salt and water into the fluid phase of the extracellular compartment, again a reasonable mechanism to support a failing circulation (70, 73). Many of the fluid shifts detected by the inulin method have been confirmed by clinical observations which have recorded sudden appearance and disappearance of edema in the absence of comparable changes in exogenous salt balance or body weight (84, 85).

The salt and water which is apparently available to the ultrafiltrate fluid phase of the extracellular compartment may be derived from the solid phases of the extracellular compartment, the fluid contained within the gastro-intestinal tract, lumina of secretory glands, etc. and the cells. It has been shown that sodium may be transferred from bone into the ultrafiltrate fluid phase by dehydration and acidosis (86). Whether chloride may be similarly supplied from the solid phase of connective tissue by alkalosis, or whether under certain circumstances sodium and chloride may be supplied simultaneously from bone and connective tissue, respectively, remains to be seen. If this sodium and chloride of the solid phase is bound or chemically associated in some way with the underlying protein medium, such a shift of these molecules into the fluid phase would conceivably elevate their osmotic activity and thereby secondarily evoke a shift of intracellular water into the extracellular fluid phase. Thus, though no single source of isotonic salt may exist outside of the fluid phase of the extracellular compartment, the possibility that sodium and chloride may be derived from different sources with the water merely shifting to maintain osmotic equilibrium would explain how endogenous isotonic expansions of the inulin space may occur.

This hypothesis, that inulin and other molecules which have the same volume of distribution delineate the ultrafiltrate fluid phase of the extracellular compartment, and that the excess electrolytes stored in the solid phase act as a buffer for the homeostatic control of the volume of the fluid phase, is admittedly unproved. It would serve, however, to explain many of the discrepancies noted in simultaneous determinations of changes in the chloride and inulin spaces.

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PERFORATION OF THE PYRIFORM SINUS; A SEQUELA OF ENDOTRACHEAL INTUBATION*

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This paper records a hitherto unreported complication of blind nasal endotracheal intubation: perforation of the pyriform sinus. The literature reveals comparatively few major traumatic sequelae of endotracheal intubation. There is, however, good reason to suspect that the true incidence of such complications is considerably higher than reported. Thus, a recent review of the literature lists 25 cases of vocal cord granulomata (1); yet, in a wide survey, otolaryngologists report 101 vocal cord granulomata following intubation for anesthesia (2).

Anesthesiologists differ in their attitude toward blind nasal intubation. Gillespie (3), a proponent of this technique, finds it difficult to imagine how a rubber tube could inflict damage in the pharynx or larynx. James (4) feels, on the other hand, that blind intubation is inexcusable except in special cases where the laryngoscope cannot be used. In the above-mentioned survey, 90 per cent of the otolaryngologists condemn the use of blind intubation.

It is beyond the purpose of this paper to examine these differences. One should emphasize, however, the hazards of potential trauma in blind intubation and urge meticulous care in this anesthetic technique.

CASE REPORT

N. L., MSH #602545, a man aged 57, was admitted to the Mount Sinai Hospital on October 13, 1949. His illness began two months previously with mental confusion, disorientation and left hemiparesis. Six weeks before admission he developed a productive cough. There was a past history of epigastric distress relieved by antacids.

Examination:—On admission, the patient was apathetic and showed marked retardation of psychomotor activity. The heart was enlarged and the pulse was regular in rate and force. Coarse rales and rhonchi were heard in all lung fields. Neurologic examination showed a left spastic hemiparesis and papilledema of the left optic disc.

Laboratory Findings:—A chest roentgenogram showed considerable enlargement of the heart and increased markings in the bases of both lungs. An electroencephalogram suggested the presence of a right frontal lobe neoplasm.

Course:—The clinical impression was that the patient had an expanding lesion of the right inferior fronto-temporal region and chronic bronchiectasis. On October 18, 1949, the patient was prepared for a subtemporal decompression. Preanesthetic medication consisted of scopolamine hydrobromide (0.4 mg.) and amytal (250 mg.). After the nose, pharynx and larynx were anesthetized with 5 per cent cocaine, a soft Magill endotracheal tube was inserted blindly into the trachea with some difficulty; an initial attempt was unsuccessful. The intubation was performed in order to have a satisfactory airway if general anesthesia was required. Under local infiltration anesthesia with 1 per cent procaine hydrochloride, a subtemporal decompression was carried out. A biopsy specimen was taken from a mass, presumably metastatic, in the right temporal lobe.

The immediate postoperative period was satisfactory until the second day when the patient's temperature rose to 101–103° F. On the fourth postoperative day the patient had

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dysphagia and expectorated large amounts of gray, mucopurulent material. The dysphagia and productive cough persisted through the remainder of the illness.

On November 1, 1949, a craniotomy was performed under local infiltration anesthesia supplemented with intravenous pentothal sodium. A mass in the right temporal lobe was excised. The patient's condition was good for four days. On the fifth postoperative day, the patient suddenly became stuporous, dyspneic and cyanotic; coarse bubbling rales were heard in all lung fields. Repeated tracheobronchial suction with a catheter and bronchoscope were ineffective. The patient died 1 hour after the onset of the stupor and cyanosis.

Post Mortem Report (§ 14461):—In the right paratracheal region, communicating with the posterior portion of the right pyriform sinus by a small round 3 mm. perforation was a large, poorly delineated abscess cavity. The latter contained approximately 75 cc. of foul, thick grayish pus. The abscess cavity dissected through tissue planes anteriorly to involve the larynx and posteriorly around the tracheal cartilages; it extended superiorly and retropharyngeally almost to the base of the sphenoid bone. The tissue in the affected area was gray and necrotic. The fascial planes were widely separated. The esophagus and mediastinum were not involved. The vocal cords were thickened; grayish white plaques were noted on their surface. The mucosal surface of the right pyriform sinus was dull gray in color and lacked normal lustre.

Confluent bronchopneumonia of the left lower lobe, perforated peptic ulcers of the duodenum and arteriosclerotic heart disease were noted.

DISCUSSION

The perforation of the pyriform sinus was an unexpected post mortem observation. A less stuporous patient might have exhibited some symptoms and signs of the neck infection. The question arose whether or not the perforation contributed to the patient's death; this could not be answered.

It must be assumed that direct trauma to the pyriform sinus, during the initial attempt at blind intubation, was the precipitating cause of the perforation. The site of the perforation indicated that the tip of the endotracheal tube lacerated the mucosa of the pyriform sinus. The perforation occurred probably in the early postoperative period rather than at the time of intubation.

Many factors, local and constitutional, have been regarded as potential and actual contributory causes of pharyngotracheal damage following intubation (5). Pneumonia, bronchiectasis, acute and chronic tracheobronchitis and deformities of the larynx and trachea have been recognized as local factors which predispose to postintubation sequelae. Constitutional disturbances, such as chronic illness, debility, dehydration, anemia, vitamin deficiency, hypoxia and advanced cardiorenal disease, have been similarly implicated.

In this case, there were several factors which caused the perforation of the pyriform sinus. Direct trauma, the exciting cause, resulted in an ulceration of the epithelium of the pyriform sinus. A pre-existing infection of the respiratory tract, as evidenced by the chronic, productive cough established a local inflammatory process which spread through the wall of the larynx into the paratracheal region. Debility, anemia, vitamin deficiency and low grade hypoxia in the immediate postoperative period may have contributed to and favored the spread of the infection through the wall of the pyriform sinus.

SUMMARY

A case of perforation of the pyriform sinus following blind endotracheal intubation is reported.

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CORRELATION OF DENTAL ABNORMALITIES IN HYPO-PITUITARISM

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Deficiency of the anterior lobe of the pituitary gland in early childhood can manifest itself in the following dentofacial conditions (1):

1. Lack or delay in development and growth with marked retardation in the cranium and face.
2. Delay in eruption, prolonged retention, and partial ankylosis of deciduous teeth with retardation of formation and eruption of permanent teeth.
3. Persistence of juvenile dental characteristics; varied disturbances in growth of alveolar bone. Disturbed contour in root surfaces and pulpal outline. Histopathologic changes may be recognized in the dental tissues. Abnormally dense calcification of dentin. Small sized roots, parallel pulpal walls, wide pulps and retardation in closure of the apical foramina.
4. Tendency toward development of deep overbite (closed bite).
5. Crowding of teeth. In some cases, the teeth may be small and crowding is not present. This is especially true when the endocrine deficiency is of congenital origin.

Thyroid, parathyroid, pituitary and other endocrine dysfunctions appear as constant underlying etiologic factors in many types of dental malocclusion. Some dental and dentofacial disturbances are regarded as pathognomonic of certain endocrinopathies (2).

Comroe, Collins and Crane (3) state that children with hypothyroidism constitute a large percentage of the patients requiring orthodontic treatment because of their abnormal jaw development and disturbed eruption. The particular type of physical deformity manifested depends on the stage of development taking place at the onset and during the time of the endocrine dysfunction (4).

In cases of growth failure which present retardation in skeletal development, as shown by prolonged delay of epiphyseal closure, a differential diagnosis should be established to rule out delayed dental development of constitutional origin, especially in the absence of definite symptoms of endocrine disturbance. Although the formation, development and eruption of the teeth can be influenced by endocrine dysfunction, the dentition is not to be accepted as a sole pathognomonic sign. Other diagnostic criteria must be relied upon in establishing a diagnosis of endocrine dysfunction.

The relationship of endocrine dysfunction to the etiology of malocclusion must

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be regarded from the standpoint of hereditary influence, congenital factors and postnatal causes. Dentofacial disharmonies should not be attributed to endocrine dysfunction without proper diagnosis.



FIG. 1. (Upper left) Full-face view of patient J. M. at age 15 years 1 month; hypopituitarism, showing characteristic immature facial features. (Lower left) Profile view. (Upper right) Full-face view of brother, A. M., age 10 years 4 months, medical history negative, showing normal facial development. (Lower right) Profile view of A. M.

CASE REPORT

History: J. M., a boy, aged 15 years and 1 month (clinic No. c-28382) was a 5 lb. 4 oz., full term baby, breech delivery. He is of Panamanian descent and was born in New York City. His mother has essentially a negative medical history and is 4' 9½" tall. His father has a history of rheumatic heart disease and is 5' 2" tall. One brother aged 10 years and 8 months, is within the normal range for weight and height. His medical history is essentially negative (fig. 1).

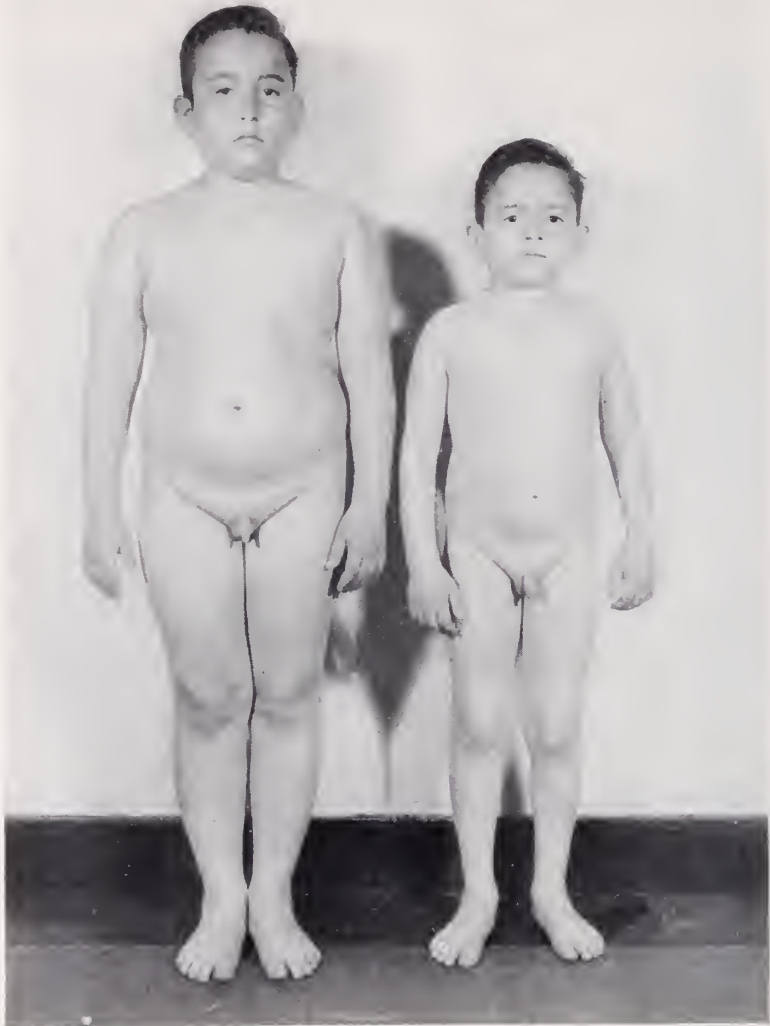


FIG. 2. (Left) A. M. brother, age 10 years 4 months of patient J. M., height is 54 inches, normal for age. Slightly obese. (Right) Patient J. M. age 15 years 4 months; height is 48 inches which is median normal for age 7 years. Patient J. M. had received thyroid therapy for previous 4 years. Patient does not show signs of normal sexual development, which usually begins at about age 12 years.

The patient was first brought to the Out Patient Department of The Mount Sinai Hospital at the age of 7 years because of his failure to attain normal growth. His mother first noticed his retarded rate of growth when he was 2 to 3 years of age. At the age of 6 years he was of the same size as his brother who was then 3 years (fig. 2).

On his entrance to the hospital, at the age of 7 years he was $40\frac{1}{2}$ " tall and weighed 37 lbs. His bone age was found to be comparable with that of a 2 year old child. He was put and kept on vitamin and thyroid therapy for about 4 years being checked periodically. During that period his height age curve deviated even more from the normal.

GROWTH IN HEIGHT AND WEIGHT BIRTH TO 17 YEARS

BOYS

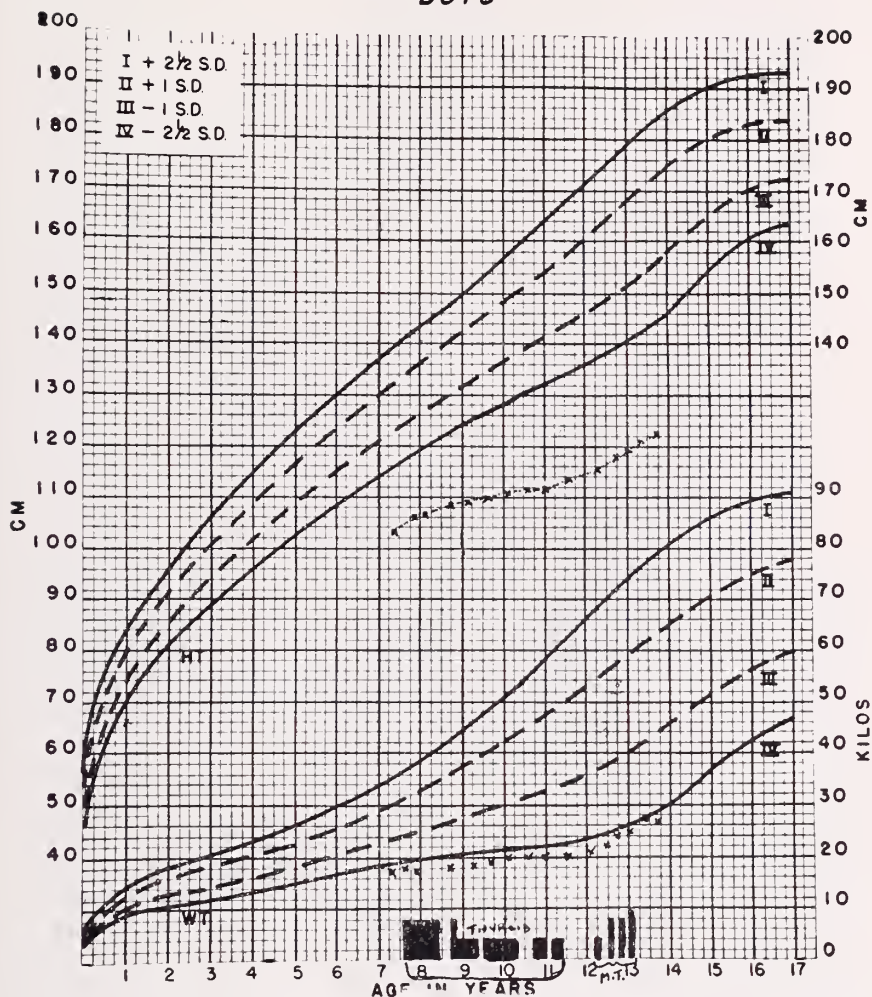


FIG. 3. Chart plotted to show standard growth in height and weight of boys from birth to age 17 years. Height of patient J. M. from age 7½ to age 14 years (broken line) is approximately 22 cm. less than the lowest quartile on the standard grid. Weight of patient J. M. (broken line) is shown to be constantly below the lowest quartile shown on grid. Bar graphs show period when patient J. M. was receiving thyroid therapy and methyltestosterone, respectively. Note marked rise in height and weight with beginning of methyltestosterone. (Courtesy of Dr. Ralph Moloshok.)

He was given a course of methyltestosterone, from March 1949 until March 1950 and responded with 24" growth in about one year. Both his height age and bone age have shown an appreciable rise since he has been receiving methyltestosterone (fig. 3).

His present health is essentially good. He is physically well proportioned. He is 48" tall and weighs 60 lb. The mean for his age is height 62" and weight 105 lb. His bone age at the present time is approximately 7 years and 6 months. He is alert and of normal mental

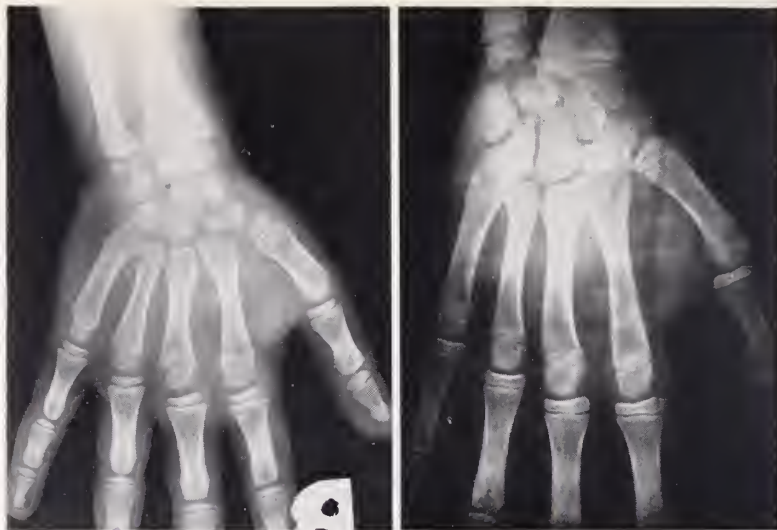


FIG. 4. (Left) Normal wrist roentgenograms of a boy at age 14 years. The spaces between epiphyses and diaphyses in the phalanges are narrow. Metacarpal epiphyses have begun union with their diaphyses. There is a definite beak on the ulnar side of the radial epiphyses. (Right) Wrist roentgenograms of patient J. M., which is similar to the standard for age 7 years. The ulnar epiphysis is just beginning to calcify. The pisiforme is still absent. The greater and lesser multangulare and noviculare are small and do not show their final forms. The epiphyses are narrower than the bones with which they will eventually unite. The spaces between the epiphyses and diaphyses are still quite wide. Note difference in size of hands.

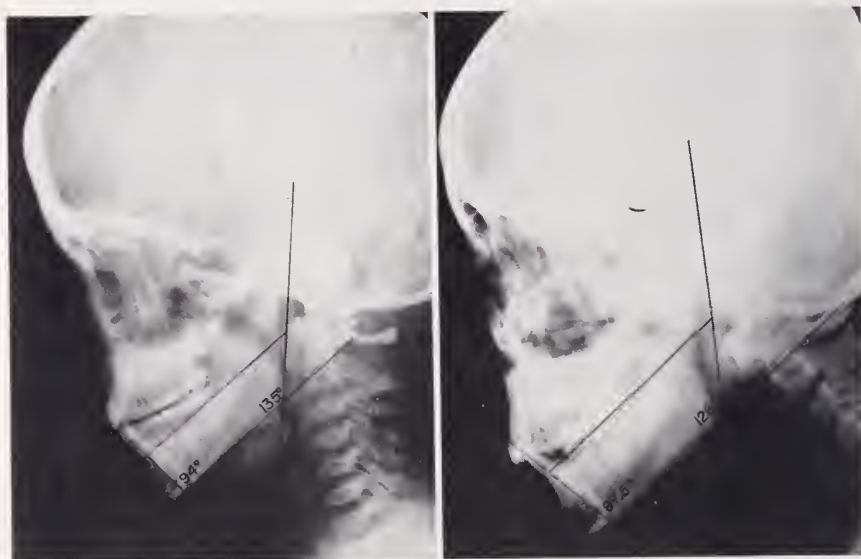


FIG. 5. Cephalostatic profile roentgenograms taken at the same target distance and reduced an equal amount for this illustration. Lines run through long axes of mandibular incisors to mandibular plane (line tangent to most dependent points on base of mandible); tangent to postcondylar point and most distal point on mandibular ramus and a line through the middle of the basal arch of the mandible (line through most constricted portion of the body of the mandible seen in profile) and parallel to the mandibular plane. (Left) Patient J. M. shows an incisor-mandibular plane angle of 94° and a gonion angle of 135° . (Right) The younger brother, A. M. shows an incisor-mandibular plane angle of 94.5° and a gonion angle of 126° . The angles are not significant. The line through the basal arch in patient J. M. is 20% shorter than that in A. M., indicating that the body of the mandible in patient J. M. who is 15 years 1 month is shorter than in his brother A. M., who is age 10 years 4 months. The relatively smaller size of the skull of patient J. M. is evident.

development. After 7 years of treatment with thyroid and methyltestosterone, he has achieved the following percentages of normal maturation for his present age: height 78 per cent; weight 57 per cent; bone age 54 per cent (fig. 4).

Cranial and facial growth of the patient show general retardation. Length of the body of the mandible is about 20 per cent less than in the brother who is over four years younger (fig. 5).



FIG. 6. (Upper) Front view of teeth of A. M., 10 years old brother of patient J. M. showing normal development for his age. (Lower) Patient J. M., showing teeth slightly separated. Dental arches show crowding of permanent incisors. There is no pathognomonic dental morphology as is often claimed. The stage of development of the dentition is equal to that of a child between $7\frac{1}{2}$ to 8 years.

His dental history reveals very marked retardation in the exfoliation of deciduous teeth and eruption of permanent teeth. According to the tables of dental eruption his dental age is now approximately 8 years.

He has a normal relationship of the upper and lower dental arches. His overbite is normal. There is a slight crowding of the anterior teeth in both jaws (fig. 6).

Roentgenograms reveal wide pulp chambers and a failure of the roots of the deciduous molars to resorb. The caries attack rate is low and the tongue and gingiva are negative (fig. 7).

His first deciduous tooth erupted at one year of age. The first mandibular molar erupted at 9 years (normal is 6-7 years) and the permanent mandibular central incisors at 10 years (normal 6-7 years). At the present time (age 15 years and 1 month) the patient shows re-

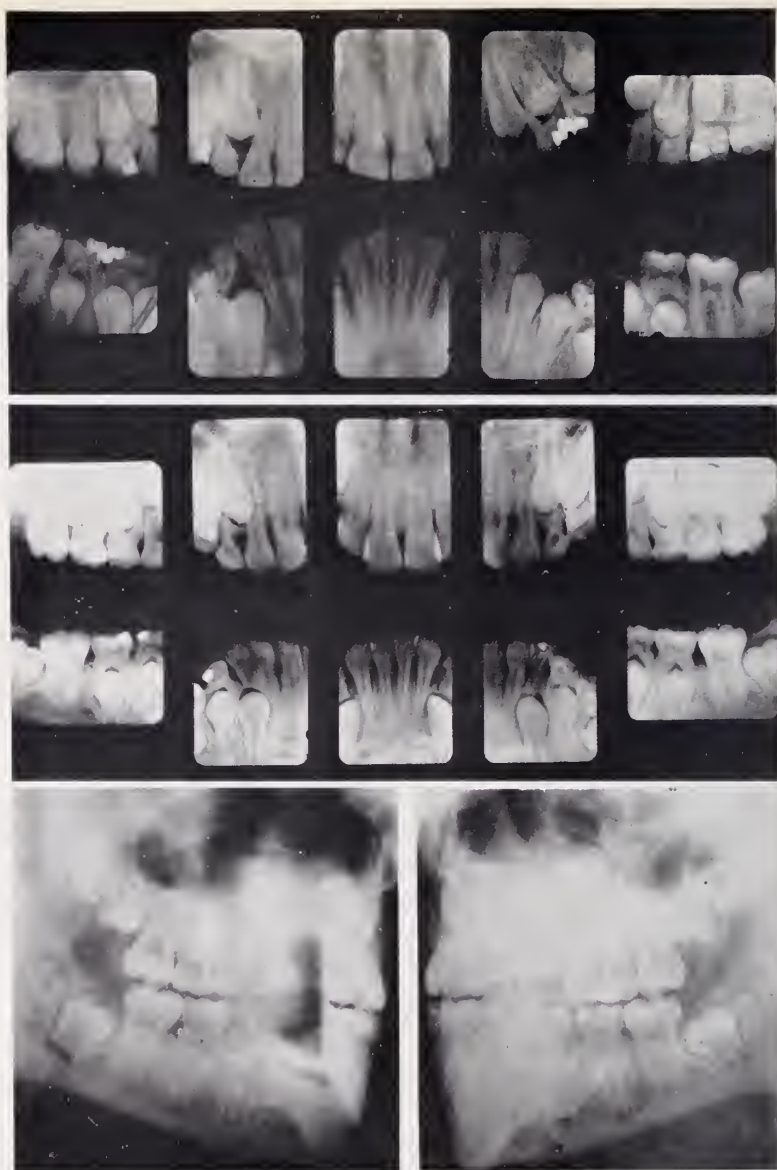


FIG. 7. (Upper) Dental roentgenograms of A. M., 10 year old brother of patient J. M., showing normal development of dentition for his age. Permanent central and lateral incisors and permanent first molars have erupted. Right deciduous mandibular canine and deciduous first molar have been exfoliated and the succeeding permanent canine and first premolar are erupting. Maxillary left second premolar has erupted. Deciduous molars show resorption of roots, prior to eventual shedding and displacement by premolar teeth. (Middle) Dental roentgenograms of patient J. M. age 15 years 1 month show dental development of about age 8 years. The pulp canals of the maxillary incisors are still open at the root apices, characteristic of hypopituitarism. The deciduous molars show failure of root resorption, although calcification of the premolars is from two-thirds to three-quarters completed. (Lower) Lateral jaw roentgenograms of patient J. M. at age 15 years. In this disturbed pattern of dental development due to hypopituitarism, the mandibular third molars are situated in the body of the mandible—past the inner angle of the ramus and body of the mandible—which is usually not found before age 15 years. The permanent second molars are still unerupted and the deciduous molars show failure of root resorption, although the roots of the premolar teeth are about two-thirds to three-quarters calcified. (Middle) Casts of patient J. M. The mixed dentition characteristic of a child around age 7 to 8 years is present, although the patient is age 15 years and 1 month of age. There is slight crowding in the incisor region.

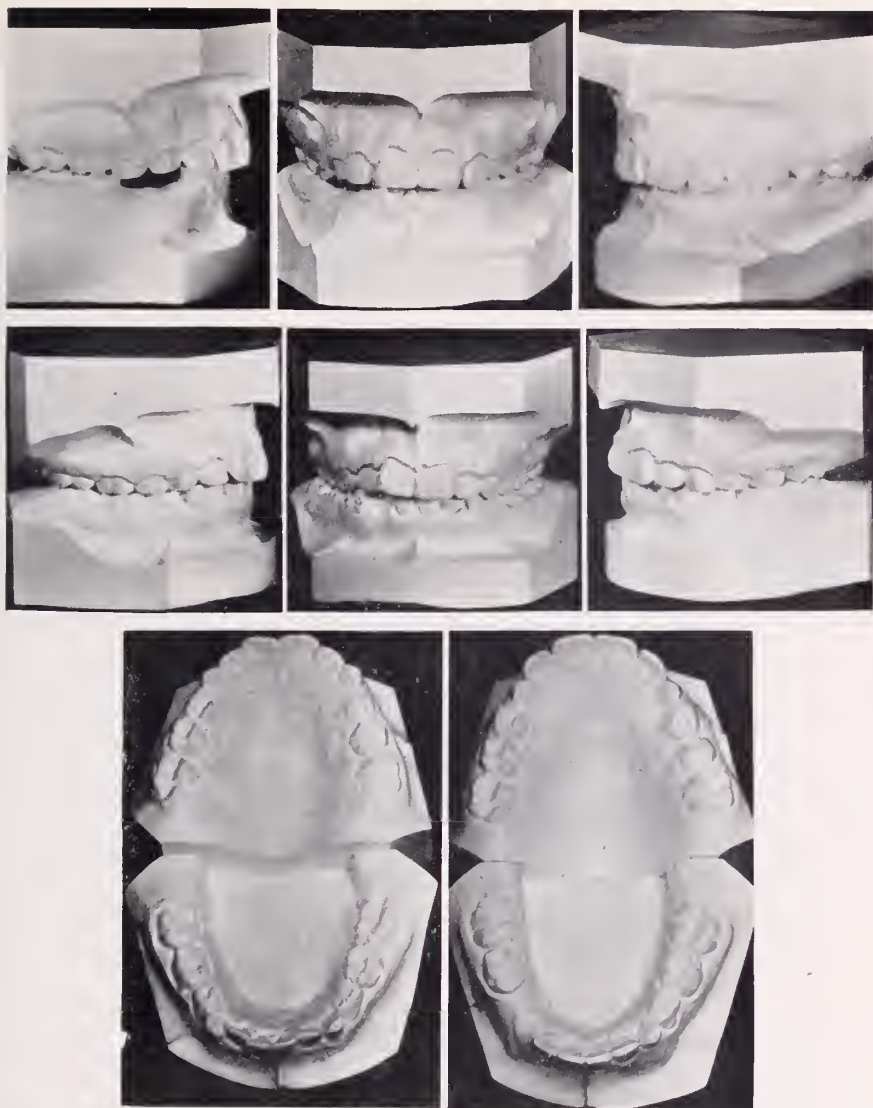


FIG. 8. (Upper) Casts of A. M., brother of patient J. M., showing normal development for his age. The slight overbite of the incisor teeth may be considered an aspect of dental arch development, until the eruption of the permanent second molars and premolars. (Lower left) Occlusal view of casts of patient J. M., showing deciduous canines and deciduous molars in position. Permanent second molars, which erupt about age 12 years, are still unerupted in this patient who is over age 15 years. (Lower right) Casts of A. M. showing well developed dental arches. The maxillary left second premolar has erupted and the lower right deciduous canine and first molar have been lost and the space for the oncoming permanent teeth shows self-maintenance.

tention of all mandibular and maxillary deciduous cuspids, and first and second deciduous molars (fig. 8).

Comment: The patient shows dwarfism and retardation of dental development. The administration of thyroid hormone is known to accelerate dental development and eruption. Although this patient received thyroid therapy for a period

of 4 years, his dental development is still extremely retarded and is following a disturbed pattern in which various stages of dental development are present simultaneously. For example, he shows absence of resorption of the deciduous canines and deciduous molar roots, which is found in children from age 8 onward. The permanent second molars, which usually are erupted at age 12 years, are still unerupted and have cortical bone overlying their occlusal surfaces. This is usually not found after age 12 years. To the contrary, the third molars are located in the body of the mandible, which is not frequently seen before age 15 years. There is no disproportion present in the upper and lower body segments.

DISCUSSION

(By *Ralph E. Moloshok, M.D.*)

The medical literature on the subject of dwarfism is in a most confused state. There are few well studied patients followed for long periods of time or documented by detailed post-mortem examinations. The clinical classification of a patient as an example of pituitary dwarfism must be associated therefore with certain reservations, unless there is evidence of an organic lesion in the hypophyseal region, or until laboratory tests are devised for the detection of a specific deficiency of growth hormone.

Descriptions of cases considered as instances of pituitary dwarfism reveal the patients to have been of normal size at birth and to have grown in a normal manner for two or three years. There is then retardation in both growth and development so that the patient falls progressively below the mean in stature. While the configuration remains symmetrical, the proportions remain those of childhood. Skeletal maturation is retarded and epiphyseal closure is delayed. Dental development is also retarded as noted in the case presented. Sexual maturation is impaired or delayed. Puberty may occur in the twenties or later so that it is difficult to diagnose the hypogonadotrophic type until later. Since the epiphyses remain open until a late age, growth may continue beyond the usual age.

Thyroid has not produced any noteworthy results in the treatment of this variety of dwarfism. A potent growth hormone is not available commercially at present. Testosterone has been used for its non-specific anabolic effect but there is suggestive evidence that it accelerates skeletal maturation and epiphyseal closure. It is considered safe to administer testosterone when the bone age is retarded beyond the height age.

We wish to thank Dr. Ann Topper and her associates, Drs. Gertrude Felshin and Ralph Moloshok of the Growth and Development Clinic for their cooperation, especially in providing the medical data in the case presented.

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MYOMA OF THE SECOND PORTION OF DUODENUM*

CASE REPORT

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The relative infrequency of benign and malignant tumors of the small bowel has long been known. In recent years, however, with increased roentgenographic skill they are being diagnosed pre-operatively with increasing frequency. It is generally conceded that the incidence of benign tumors of the duodenum is the lowest of the entire gastro-intestinal tract. Raiford (1) observed that of all intestinal tumors, nine per cent occurred in the small intestine. Of all malignant intestinal tumors, five per cent were found in the small bowel whereas, of the benign tumors, twenty-four per cent were located there. Moore and Schmeisser (2) pointed out that fifteen per cent of benign small intestinal tumors, and nineteen per cent of small intestinal myomas occurred in the duodenum. Staemmler (3) stated that twelve per cent of small intestinal myomas were duodenal. Grayzel (4), on the other hand, who has more recently summarized his experience with duodenal tumors, gave somewhat higher figures. He stated that twenty-six per cent of all small intestinal tumors were duodenal, whereas forty-two per cent of the benign tumors were located in the duodenum.

Foerster (5), first described a myoma of the ileum in 1858. Schlatzler (6) recognized this tumor in 1871. Wesener (7) in 1883 was the first to describe a myoma of the duodenum. His case was a myoma of the second portion of the duodenum, which grew into the head of the pancreas, and produced the symptoms of weakness, anemia, weight loss, and vomiting of coffee ground material. Hertaux (8) presented thirty-two cases of small intestinal myoma in 1899, and King (9) in 1925 added ten cases of his own. Balfour and Henderson (10) reported a case of duodenal myoma in 1929. Moore, in 1934 presented forty-seven cases of small intestinal myomas, of which nine were duodenal, fifteen jejunal, nineteen ileal, and four unclassified.

Etiology: Though the infrequency of small intestinal tumors is known, no adequate explanation for it has been presented. The two major theories entertained are those of stasis, and embryonic development. The proponents of the stasis theory point to the stasis occurring in the stomach and colon, the most frequent sites of gastro-intestinal malignancy. They state that stasis is conducive to irritation, which has been offered as one of the etiological factors in the formation of neoplasms. Since there is little stasis in the small bowel one might expect a lower incidence of neoplasms. However, the terminal ileum, which is the region of greatest stasis in the entire small bowel, is the most common site of small intestinal tumors.

The embryonic theory of Cohnheim, on the other hand, emphasizes the fact that the small intestine develops during the last four months of fetal life.

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This, therefore presents a smaller opportunity for the occurrence of arrested development, and misplaced embryonic tissue.

Incidence: Of Moore's forty-seven cases, twenty-seven were male, fourteen were female, and the sex of six were not stated. Thus, there is approximately a two to one preponderance in favor of males. The age limits extended from fifteen to seventy-nine, with the average age being in the fifth decade.

Pathology: Myomas may be single or multiple, and may vary greatly in size. They may originate in the muscularis propria and grow internally, or they may originate in the outer muscular layer, and grow peripherally. Steiner (11), and Harrington (12) classified small intestinal leiomyomas on the basis of this relationship to the lumen of the bowel. They noted that outer tumors were twice as frequent as inner ones, and whereas inner tumors cause symptoms relatively early, outer ones reached larger proportions before causing symptoms. Spontaneous hemorrhage, and intestinal obstruction are the most frequent complications of each, the incidence of each being approximately sixty per cent. Cystic, and hemorrhagic degeneration of the tumors were the next most frequent complication. Section reveals the characteristic striated, or convoluted markings, caused by the intertwining of muscle bundles. The tumors are sharply circumscribed, and shell out easily. Their nutrition is maintained largely by surrounding lymph vessels. Microscopically, the cells are larger, shorter, and more rounded than normal. The nucleus is larger, stains lighter, and contains numerous chromatin particles. Supporting connective tissue, and blood vessels accompany the muscle cells.

Ewing (13) stated that there was no proof that a malignant tumor represented transformation of a previously benign one. Plenk (14) and Raiford however, have observed malignant degeneration of myomas. Raiford (15) noted that internal tumors were usually benign, whereas externally growing ones were more frequently malignant.

SYMPTOMATOLOGY

Pain: Smith (16), and Foshee (17) observed that a burning ulcer like pain might be present, and is usually associated with an ulceration of the overlying mucosa. Brechot (18) pointed out that most patients have only vague epigastric complaints.

Intestinal obstruction: This was observed by Virchow, Smith, Steiner, and others. This is the commonest surgical complication of small intestinal tumors, and is usually due to intussusception of a pedunculated submucous tumor.

Hemorrhage, which may be grave is a very frequent complication. This was noted by Cave (20), D'Allaines (21), Virchow, and others. Myomas commonly develop focal areas of hemorrhagic necrosis, which may become confluent, and discharge into the lumen. This then forms an ulcer crater which may bleed copiously, and/or cause ulcer-like pain.

Icterus, chills and fever were reported by Wendel (22). In his case, the tumor arose against the papilla of Vater, and when projected downward, occluded the papilla.

Diagnosis: The diagnosis of small intestinal myomas is difficult. Whereas duodenal tumors may be frequently diagnosed by x-ray, roentgenographic examination of the remainder of the small intestinal tract is much more difficult.

CASE REPORT

History: The patient (Adm. #630928) was a man aged 53 years, a painter by occupation. He entered The Mount Sinai Hospital complaining of paleness of the skin, 6 to 7 weeks in duration, and generalized weakness of 5 to 6 weeks' duration. He had a previous admission to another hospital in 1938. At that time he complained of epigastric distress, vague post-prandial epigastric pain, weakness, pallor, and tarry stools. The general physical examination was non contributory. The hemoglobin was 30%; red blood cell count, 2.5 million. Gastro-intestinal series revealed an irregular contour of the duodenal bulb, and a diagnosis of duodenal ulcer was made. The patient was placed on an ulcer regimen, without relief of his predominant symptoms. He had a previous admission (1941) to The Mount Sinai Hospital when he complained of palpitation, nervousness, and irritability. Hemoglobin at this time was 98%. Basal metabolic rate was plus 45. Following pre-operative lugolization, a subtotal thyroidectomy was performed.

He remained well until 7 weeks prior to his recent admission. His wife noted that he appeared pale. At this time he experienced no gastro-intestinal symptoms, and one week later he noted generalized weakness which was followed by coldness of his legs and faintness.

Examination: The patient was well developed, well nourished, and slightly obese. His lungs and heart were normal. The blood pressure was 138/74; pulse, 100. The abdomen was slightly obese. The liver was palpable at the costal margin. Rectal examination revealed no masses. Stool on the finger tip was black, and the guaiac test was 4 plus.

Laboratory findings: Hemoglobin, 8.6 Gm.; white blood cells, 8600 with a normal differential count. Urine, normal; blood urea nitrogen, 19 mg%; total protein, 7.9 Gm.; albumin-globulin ratio was 4.5/3.4. The hemoglobin rose to 12 Gm. after repeated transfusions. Fasting blood sugar, 102 mg%; bilirubin, 0.5 mg%; Vandenberg, negative; alkaline phosphatase, 9 King-Armstrong units. Stools were negative for ova and parasites; they were guaiac positive at first, but became and remained guaiac negative on repeated examinations. Rbfluss test meal, no free HCL even after histamine. Electrocardiogram: Precordial leads normal. The RS-T and T wave abnormalities may be due to myocardial involvement.

X-ray studies: Barium enema examination showed no organic lesion in any portion of the large bowel. Examination of the chest showed no abnormality in the lungs. The heart appeared somewhat enlarged in its transverse diameter. Gastro-intestinal series: Barium meal examination showed no abnormality in the esophagus or stomach. There was an ovoid filling defect in the second portion of the duodenum, mainly on its mesial aspect which measured approximately one inch in length. The mucosal folds in this vicinity appeared to be within normal limits. The inner contour of the duodenum was effaced. The change described was presumably due to an intra-luminal duodenal polypoid tumor, whether benign or malignant could not be stated with any degree of certainty.

Hematology: Hemoglobin, 8.5 Gm.; red blood cells, 3.8 million; hematocrit, 29%; white blood cells, 8300; segmented, 57; non segmented, 2; lymphocytes, 37; eosinophiles, 1; basophiles, 2; mononuclears, 1; platelets, 320,000; reticulocytes, 3.4%; mean corpuscular volume 76; mean corpuscular hemoglobin, 23; mean corpuscular hemoglobin concentration, 29.5. There was anisopoikilocytosis, polychromasia, basophilic stippling with reticulocytosis. There was also hypochromia, and microcytosis, consistent with an iron deficiency anemia; active regeneration, consistent with chronic blood loss. Bone marrow aspiration revealed a hypocellular marrow. There was erythroid hyperplasia with grossly deficient hemoglobinization, compatible with an iron deficiency anemia.

Operation: (October 2nd, 1951 by Dr. J. H. Garlock.) The patient was explored through a right upper rectus muscle splitting incision. The duodenum was mobilized, and a 3 x 1.5 cm. tumor of firm consistency was palpated on the medial wall of the second portion of the

duodenum, in the general vicinity of the ampulla. The second portion of the duodenum was opened, and the tumor area delivered through the opening. A circular incision was then made in the mucosa at the base of the tumor, which was then shelled out from the duodenal wall. Hemostasis was obtained, and the mucosa was closed with a continuous chromic suture. The common duct was now explored, in order to demonstrate patency of the near-by papilla. The latter was found to be uncompromised by the resection. A T-tube was inserted



FIG. 1. Filling defect on the mesial wall of the second portion of the duodenum

into the common duct and the duodenum was closed transversely in two layers. Two Penrose drains were inserted to Morrison's pouch, and the wound was closed.

Pathology: Specimen consisted of a 2.9 x 1.5 x 1 cm. roughly cylindrical shaped mass of tissue, stated to be from the duodenum, and received in fixative. There was a 2 x 1 cm. area on one surface, which had the appearance of duodenal mucosa, in the center of which, there was a 3 mm. sharply punched out area of ulceration. Microscopic revealed a myoma of the duodenum, with ulceration of the overlying duodenal mucosa.

Postoperatively the patient ran a temperature of 102°F. to 103°F. for the first four

postoperative days. This was associated with several transient episodes of flutter fibrillation, which reverted to regular sinus rhythm. His temperature subsided to normal by the sixth postoperative day, where it remained for the remainder of his postoperative course. A cholangiogram on the ninth postoperative day revealed good filling of the biliary radicles, with prompt entrance of the lipiodol into the duodenum. The T-tube was removed. The patient was readmitted to the hospital two months after discharge for re-evaluation. Barium meal at this time showed no intrinsic abnormality of the esophagus, stomach or duodenum. The duodenal curve was normal in appearance. Stools were guaiac negative, and the patient's hemoglobin was maintained at 12.5 grams%.

DISCUSSION

This case emphasizes the difficulty encountered in making a correct diagnosis of duodenal myoma. The patient first presented himself with vague epigastric complaints and anemia, at which time x-rays revealed an irregular contour of the duodenum, suggesting a duodenal ulcer. Eight years later, the patient again presented himself with the symptoms of severe anemia, which was proven to be caused by gastro-intestinal bleeding. At this time the diagnosis was made roentgenographically. Despite the length of time which had elapsed between the onset of symptoms, and operation, no evidence of malignant transformation was demonstrated in the specimen.

CONCLUSIONS

1. Nine per cent of all gastro-intestinal tumors are of small bowel origin; five per cent of malignant tumors, and twenty-four percent of the benign tumors are located there.

2. The etiology, incidence, pathology, symptomatology, and diagnosis of duodenal myomas are discussed.

3. A case of bleeding myoma of the second portion of the duodenum, with positive x-ray findings, is presented.

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EPILEPSY AND THE ELECTROENCEPHALOGRAM*

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The most important clinical application of the electroencephalogram is either to confirm or rule out the existence of an epileptic disorder. The fact that normal records do occur in known epileptics is disturbing not only to the clinician but also to the electroencephalographer. This disturbing feature, however, can be reduced in its significance by familiarizing oneself with the various clinical and historical features associated with normal and abnormal records. To ascertain some of these features I studied 100 epileptics, varying in ages from 5 to 73 years, in the out-patient department of this hospital. I classified these patients according to the type or types of seizures from which they suffered, namely, grand mal, petit mal, psychomotor or focal.

TECHNIQUE AND METHOD

Standard records were taken with a 6 channel electroencephalograph. The technique employed was similar to that described in a previous article (8). All recordings were routinely taken with the patient fully awake and in a non-fasting state. Other than hyperventilation, no provocative techniques such as sleep (natural or induced), metrazol, photic stimulation, hydration, etc. were employed. Initial records were taken following the withdrawal of all medication for at least 48 hours. A second recording was made after the patient had been under anticonvulsant therapy for at least 6 to 12 months. The records thus obtained were then classified according to the type of EEG abnormality, as follows: records with asymmetrical and focal delta; records with symmetrical and diffuse bursts of slow activity; with symmetrical and diffuse bursts of slow activity and spike and wave forms; with symmetrical and focal bursts of slow activity; records with diffuse slow activity; with diffuse slow activity and superimposed bursts of delta activity; and finally records with diffuse slow activity and superimposed bursts of spike and wave forms.

Patients with Grand Mal seizures only: (tables I, II, III) There were 63 cases suffering from grand mal seizures only. Their attacks were characterized by an abrupt onset, loss of consciousness, followed by generalized tonic and clonic movements. In 6 cases the loss of consciousness was followed by a generalized increase in tonus without any clonic movements. Auras were present in 12 cases and they included epigastric sensations, dizziness, fear, palpitation, head noises, deafness, choking sensations, flashes of light and spots before the eyes. Of the 63 patients, 23 or 33% had normal records and included 4 or 20% of the 19 cases who had their first seizure before the age of 10 years, 4 or 20% of the 19 cases who had their first seizure before the age of 20 years, 6 or 60% of the 10 cases who had their first seizure before the age of 30 and finally, 9 or 80% of the 11 cases who had their first seizure after the age of 40. Of the 63 cases there were 40 or 67% with abnormal EEGs. These included 26 (40%) with diffuse and symmetrical bursts of slow activity; 6 (10%) with diffuse and symmetrical bursts of delta waves and spike and wave forms; 1 (2%) with diffuse slow activity and symmetrical bursts of spike and wave forms; 2 (4%) with asymmetrical and focal delta activity; 2 (4%) with diffuse slow activity; 2 (4%) with diffuse slow activity and superimposed symmetrical and diffuse bursts of delta waves and finally 1 (2%) with symmetrical and focal bursts of slow waves. Following the administration of anticonvulsant drugs the number of normal records in patients with grand mal only rose from 23 or 33% to 38 or 60%.

Patients with Grand Mal and Focal seizures: (tables I, II, III). Twenty-three patients

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suffered from focal and generalized convulsive seizures. Sometimes the grand mal seizures began abruptly without a focal onset. At other times they would begin focally and terminate in a generalized seizure. Focal motor seizures were present in 17 cases and were characterized by a turning of the head, eyes and sometimes of the body in 7; by twitching of one side of the face, the mouth, an arm, a foot or one entire side of the body in 10 cases. Focal sensory seizures were present in 5 cases and included parasthesia of an extremity in one,

TABLE I
Relation between EEG abnormality and type of clinical seizures

EEG	GM ONLY	PM; PM & GM PM; GM & FOCAL; PM, GM & PSY- CHOMOTOR	GM & FOCAL	GM & PSY- CHOMOTOR	FOCAL	TOTAL
N.....	23(33%)	0	9(40%) ^h	3(60%) ^m	1	36
BS-D.....	26(40%) ^{a, b}	1(12%)	7(30%) ⁱ	2(40%)	0	36
BS-D sw.....	6(10%) ^c	7(88%) ^g	3(13%) ^j	0	0	16
BS-F.....	1(2%)	0	0	0	0	1
D.....	2(4%) ^d	0	0	0	0	2
D, BS-D.....	2(4%)	0	1(4%) ^k	0	0	3
D, BS-D sw.....	1(2%) ^e	0	0	0	0	1
F.....	2(4%) ^f	0	3(13%) ^l	0	0	5
Total.....	63	8	23	5	1	100

B—bursts; S—symmetrical; D—diffuse; sw—spike and wave forms; F—focal; N—normal.

^a three cases gave a history of febrile convulsions in infancy or early childhood.

^b in one case the bursts were most prominent at both frontal areas and in another case the bursts were shifting in character accentuated at times more on one side than the other.

^c in one case the bursts were at times diffuse and symmetrical and at other times most prominent at both frontal areas.

^d one case was diagnosed as birth trauma.

^e asymmetrical bursts of spike and wave forms were also present.

^f one patient had a brain tumor. A second recording of the other patient was normal.

^g two cases gave a history of febrile convulsions.

^h one case followed a blast concussion with a period of unconsciousness lasting for days.

ⁱ x-ray examination showed calcification over the motor cortex in one case. Another suffered a fractured skull with subsequent craniotomy.

^j one case had cerebrocerebellar dysgenesis, a second had encephalitis with residual hemiparesis. The third case showed bursts of spike and wave forms at times symmetrical and diffuse and at other times more pronounced over one hemisphere.

^k post encephalitis.

^l cerebral thrombosis with hemiparesis and aphasia in one, brain tumor in another.

^m in one case seizures followed a removal of a Gasserian ganglion tumor.

a homonymous quadrantanopsia in one, attacks of dizziness in one, visual and auditory hallucinations in two. Finally, one patient suffered from seizures characterized by attacks of abdominal pain in addition to generalized convulsions. Of the 23 cases, 9 or 40% had normal EEGs and included 2 or 25% of the 8 patients with onset of seizures before the age of 10 years; 2 or 40% of the 5 patients with onset of seizures before the age of 20; and 5 or 50% of the 10 cases with an onset of seizures beyond the age of 20. Of the 23 cases there were 14 or 60% with abnormal records. These included 7 (30%) with diffuse and symmetrical bursts of slow activity; 3 (13%) with diffuse and symmetrical bursts of delta activity and

of spike and wave forms; 1 (4%) with diffuse slow activity and superimposed symmetrical and diffuse bursts of delta waves and 3 (13%) with asymmetrical and focal delta activity. Following the administration of anticonvulsant drugs the number of normal records rose from 9 or 40% to 15 or 65%.

TABLE II
Relation between EEG abnormality and age of onset clinical seizures

TYPES OF SEIZURES	TOTAL NO. CASES	TOTAL NO. CASES IN AGE GROUPS WITH NO. OF NORMALS WITHIN EACH GROUP				
		1-10	10-20	20-30	30-40	40 & over
GM	63	19 4(20%)	19 4(20%)	10 6(60%)	4 0	11 9(80%)
GM & Focal	23	8 2(25%)	5 2(40%)	2 1(50%)	2 1(50%)	6 3(50%)
PM; PM&GM; PM, GM&Foeal; PM, GM, & Psychomotor	8	6 0	2 0			
GM&Psychomotor	5		1 0	1 1(100%)	1 1(100%)	2 1(50%)
Focal	1			1 1(100%)		
Total	100					

TABLE III
Relation between EEG abnormality and type of clinical seizures following intensive anticonvulsant therapy

EEG	NO. CASES GM ONLY	NO. CASES PM; PM & GM; PM, GM & FOCAL; PM, GM & PSYCHOMOTOR	NO. CASES GM & FOCAL	NO. CASES GM & PSYCHOMOTOR	NO. CASES FOCAL	TOTAL
N	38(60%)	1(12%)	15(65%)	3(60%)	1	58
BS-D	20(32%)		3(13%)	2(40%)		25
BS-D sw	2(4%)	7(88%)				9
BS-F						0
D	1(2%)		1(5%)			2
D, BS-D						0
D, BS sw	1(2%)					1
F	1(2%)		4(17%)			5
Total	63	8	23	5	1	100

Patients with Petit Mal alone or combined with other types of seizures: (tables I, II, III). Eight cases suffered from petit mal seizures either alone or combined with one or more other types of seizures. The petit mal attacks were characterized by a momentary loss of consciousness with or without fluttering of the eyelids, myoclonic jerks or loss of postural tone. The records of all 8 cases were abnormal. One showed diffuse and symmetrical bursts of slow activity and 7 this abnormality with superimposed symmetrical and diffuse bursts of spike and wave forms. The onset of seizures in 6 cases was before the age of 10 and in 2 before twenty. With anticonvulsants the record of only one case became normal.

Patients with Grand Mal and Psychomotor seizures: (tables I, II, III). There were only

5 cases with grand mal and psychomotor seizures. In all instances the psychomotor seizures were characterized by periods of automatisms with repetitive, purposeful but poorly coordinated movements followed by partial or complete amnesia for the attack. Three or 60% of the 5 cases had normal EEGs; 2 showed symmetrical and diffuse bursts of slow activity. The age of onset in 4 cases was over 20 and the records of three of them were normal. The age of onset in the fifth case was under 20 and the record of this patient was abnormal. Following prolonged anticonvulsant therapy the records of these same 100 patients showed the following: (table III) 58 were normal, 25 showed symmetrical and diffuse bursts of delta activity, 9 showed symmetrical bursts of spike and wave forms, 2 diffuse slow activity, 1 diffuse slow activity with superimposed symmetrical and diffuse bursts of spike and wave forms and 5 focal abnormalities. The normal records included 38 (60%) of the 63 cases with grand mal seizures only; 1 (12%) of the 8 cases with petit mal attacks; 15 (65%) of the 23 cases with grand mal and focal seizures, and finally, the single cases with focal seizures only.

Of the 100 epileptics there were 8 who gave a history of seizures among their near relatives. Only one of them suffered from petit mal, yet the records of 7 were abnormal.

COMMENT

Jasper and Kershman (5) in a series of 494 epileptics observed normal records in 26 or approximately 5% of the cases. Gibbs, Gibbs and Lennox (2) in a series of 1260 epileptics found normal records in 164 or approximately 13%. In a later series, Gibbs and Gibbs (3) found normal records in 64% of their cases most commonly in patients with grand mal seizures only and least often in patients with petit mal either alone or in combination with one or more other types of seizures. Abbott and Schwab (1) in a series of 193 epileptics found normal records in 40 or 20%. Lennox *et al.* (7) observed that anticonvulsants modified but did not completely abolish EEG abnormalities in epileptics. Jasper (5) observed that although anticonvulsant drugs modified clinical seizures they did not necessarily abolish any pre-existing EEG abnormality but as a rule did tend to diminish them. Abbott and Schwab (1) observed a diminution and in a few instances a complete abolition of the EEG abnormality during anticonvulsant therapy. Gibbs and Gibbs (3) believed that anticonvulsants seldom altered abnormal EEG activity. Hoefer *et al.* (4) observed a diminution in the degree of EEG abnormality in adequately treated epileptics. Lennox (6) observed a correlation between clinical improvement and a lessening in the degree of EEG abnormality following anticonvulsant therapy. Abbott and Schwab (1) found a high percentage of abnormal records in epileptics with a history of seizures during infancy. They found normal records in patients with infrequent seizures and in cases having only nocturnal seizures. Lennox (6) found 4 times as many abnormal records in patients who had their first seizures before they reached the age of 20 as in those who had their first seizures later in life. Gibbs (3) noted that the greater the frequency of clinical seizures the greater the number of abnormal records found. From our observations a normal record in patients with a familial history of epilepsy, irrespective of the type or types of seizures, is most unusual. In the absence of a familial history of epilepsy we noted a definite correlation between the type of clinical seizures and the EEG, in that patients suffering from grand mal seizures only or combined with focal seizures are apt to have normal records. In evaluating a record therefore, it is

essential to know which type or types of seizures one is dealing with for, while a normal record does not eliminate a diagnosis of epilepsy in a patient with grand mal or grand mal mixed with focal seizures, it does render such a diagnosis most improbable in patients with petit mal. Conversely, a normal record in a patient with a history suggestive of petit mal casts a good deal of doubt upon a diagnosis of epilepsy.

A correlation exists between the age of onset of the first seizures and the EEG in that the older an epileptic is at the time of the first seizure the more likely it is for the patient's EEG to be normal.

As for the administration of anticonvulsant drugs, they have in many instances completely abolished pre-existing abnormalities in the EEG, rarely however, in patients with petit mal.

No definite relationship could be established between the EEG and the number or frequency of clinical attacks before or after the use of anticonvulsants despite the fact that in the majority of instances clinical improvement was attained with the use of these drugs. Any demonstrable relationship proved to be only a statistical one and was not necessarily true in each case. For example, in certain adequately treated cases the EEG continued to be abnormal although the interval between seizures increased to a year or more, while in other instances, where the attacks were reduced to one a month or one in two months, the EEG abnormality completely disappeared.

As to the time of day of seizures and its relationship to the EEG, normal records were just as frequent in patients having nocturnal seizures as in patients with diurnal seizures. For example, in patients with grand mal only, of 19 cases with chiefly nocturnal seizures 6 or 33% had normal EEGs and of 44 cases with chiefly diurnal seizures 17 or 37% had normal records. In patients with grand mal and focal seizures, of 5 cases with chiefly nocturnal attacks the records of 2 or 40% were normal and of 18 cases with chiefly diurnal attacks the records of 7 or 40% were normal.

Finally, no correlation was observed between the age of the patient at the time of recording or the duration of illness and the EEG.

CONCLUSIONS

1. Irrespective of the type or types of seizures from which they suffered, patients with near relatives suffering from epilepsy rarely showed a normal electroencephalogram.

2. In the absence of any familial history of epilepsy, a normal electroencephalogram was frequently encountered among epileptics, irrespective of the type or types of seizures providing the seizures did not include petit mal.

3. The earlier the age of the onset of seizures the greater the likelihood of the presence of an abnormal electroencephalographic record.

4. Anticonvulsants decreased the number of abnormal electroencephalographic records.

5. In this study no correlation was found between the EEG and:

- a) Frequency of seizures;

- b) Age at the time of recording;
- c) Duration of illness;
- d) Time of day of attacks; or
- e) Any combination of types of seizures providing they did not include petit mal.

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ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS
OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out patient department of the Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

Skin Reactions. XVII. The Stability of Glycerite of Hydrogen Peroxide on the Human Skin.

H. A. ABRAMSON. J. Invest. Derm., 15: 19, July, 1950.

Activity of the human skin with respect to peroxide decomposition has been studied by means of films of glycerite of hydrogen peroxide. Peroxide activity in the films was followed by means of starch iodide paper. It was found that in the normal human skin of the forearm peroxide activity remained in the films of peroxide for at least 90 minutes. Similar results were obtained in the palm of the hand and over psoriatic lesions. Decomposition was about twice as fast between the toes. Thin films of glycerite of hydrogen peroxide are fairly stable reservoirs of peroxide on the human skin but the rate of decomposition depends upon a complex number of factors including the viscosity of the glycerine, acidity, the presence of moisture, and the presence of catalysts like catalase. The method may probably be applied to the detection of catalase in the dermatoses.

Psychotic Factors in Psychosomatic Illness. JESSE APPEL, AND SAMUEL RICHARD ROSEN.

Psychosomatic Med., 12: 236, July-August, 1950.

The authors postulate that a reciprocal relationship exists between the so-called physical manifestations of psychosomatic illness and the psychologic manifestations of psychiatric illness. In 4 patients being treated for psychosomatic disturbances, psychotic features appeared. It seemed significant that concomitantly the somatic disturbances tended to decrease or disappear. Accordingly, it was suggested that the psychosomatic disorder, in certain types anyway, might represent a manifestation of the underlying conflict seen in some of the psychoses. In one of the cases it was found that it was possible to bring about several reversals of the somatic-psychotic alternating pattern. One chronic rheumatoid arthritis and 2 chronic ulcerative colitis cases illustrated the reciprocal relationship, while, in the case of chronic bronchial asthma, both somatic and psychotic symptoms tended to overlap each other in time sequence. A warning is issued, in view of the sudden changes in psychosomatic disorders occurring in ACTH and cortisone therapy, that the possibility of complicating psychoses be considered.

Surgical Complications of Congenital Anomalies of the Umbilical Region. E. E. ARNHEIM.

Surg. Gyn. & Obst., 91: 71, July, 1950.

The embryologic, pathologic, and clinical features, and the treatment of the surgical complications of omphalocele and patent omphalomesenteric duct are reviewed. Recoveries are reported in 1 case of rupture of an omphalocele sac, and in 1 case of prolapse of the ileum through a patent omphalomesenteric duct; the latter is the fourth reported cure of this condition. The successful treatment was based upon a combination of early operation, careful operative technique, and adequate preoperative and postoperative management. These measures enabled the infant with a ruptured omphalocele to survive 2 intestinal resections in the first 3 days of life.

Determining Factors in Composing and Analyzing Speech-Hearing Tests. WILLIS C. BEASLEY, AND HARRY ROSENWASSER. *Laryngoscope*, 60: 658, July, 1950.

A new kind of speech-hearing test, known as the Beasley Differential Speech-Hearing Test, is described. This test is composed of monosyllabic words of the consonant-vowel-consonant type, which are divided into two lists on the basis of the energy-frequency char-

acteristics of the phonetic elements. The words in the two list are designated as low frequency (LF) and high frequency (HF) words. The initial and final consonants in these words contribute more than the vowels to the differentiating efficiency of the test, and hence, scoring is based upon perception of consonants. The test is organized and administered in such manner that two articulation curves result: one for LF and one for HF phonetic elements. This test was given to 850 patients, of whom about 500 had hearing impairments ranging from slight to very severe. In addition, pure tone audiograms by air and bone conduction were obtained routinely on each patient. A prolonged series of tests were given to 50 normal subjects as a control for comparison with the patients' data.

In this report, the data were analyzed by a group trend method to determine whether the HF and LF articulation curves bear any consistent relationship to the pattern of pure tone audiograms. The results, as depicted in 12 charts based upon statistical calculations for grouped data, indicate consistently that: A. For the subjects having normal pure tone audiograms, there is no significant difference between the positions and curvature of the LF and HF articulation curves. B. For subjects with impaired hearing, the displacement of the LF and HF articulation curves from the position of the articulation curve for normal subjects is approximately proportional (but not equal) to the average amount of hearing loss for pure tones at 1,000, 1,500, and 2,000 cycles. C. For subjects with different patterns of pure tone audiograms, the LF and HF articulation curves are displaced relative to each other in amounts and direction that are proportional to the relative average hearing loss for pure tones below 1,500 cycles (LF) and above this reference (HF).

Although these trends, which are based upon grouped data, are consistent throughout, there is a significant number of cases (approximately 28 per cent) in our records that do not conform. Prediction of speech-hearing ability from the pattern of pure-tone audiograms is not valid for individual cases. The authors expect to explore the reasons for these exceptions to the basic group trends in a subsequent analysis. The demonstrated efficiency of this particular speech-hearing test in revealing differences between the abilities to perceive low frequency and high frequency phonetic elements of speech-sounds has a practical significance for the otologist, especially in evaluating end-results after the fenestration operation for clinical otosclerosis. Similarly, this differential speech-hearing test has a direct application to the selection of hearing aids in individual cases, and appraising the *nature* of hearing improvement accomplished by different hearing aid fittings.

Disposable Ileostomy and Colostomy Bag. ARTHUR A. GLADSTONE, AND ROBERT TURELL. J. A. M. A., 143: 894, July, 1950.

A new disposable ileostomy and colostomy bag is described and illustrated.

Acute Coronary Insufficiency: Pathological and Physiological Aspects. H. HORN, L. E. FIELD, S. DACK, AND A. M. MASTER. Am. Heart J., 40: 63, July, 1950.

A series of twenty-five cases is presented in which recent myocardial change was found in the absence of acute coronary occlusion. The lesions were confined for the most part to the subendocardial musculature and the papillary muscles of the left ventricle. They varied in extent from a few scattered microscopic foci to widespread disseminated and grossly visible areas. In seven instances almost the entire inner shell of the left ventricle was involved. The mildest changes consisted of eosinophilic smudging; granularity, uneven staining, and loss of striations of the affected myofibrils; nuclear degeneration; areas of hemorrhage and capillary engorgement. More advanced lesions showed widespread hemorrhage; disappearance of nuclei; homogenization, vacuolization, rupture of muscle fiber; and finally, focal or confluent zones of necrosis with reactive infiltration by polymorphonuclear leucocytes, lymphocytes and mesenchymal cells. Granulation and fibrous tissue characterized the older lesions. Examination of twenty-four hearts disclosed acute ischemic changes; one showed organizing lesions only. These alterations are believed to have been caused by intense myocardial ischemia due to acute coronary insufficiency. Coronary arteriosclerosis with moderate or severe narrowing was present in nineteen cases.

Twenty-two hearts were hypertrophied. Six hearts, in addition, revealed extensive fibrocalenic aortic stenosis; one mitral stenosis; one syphilitic aortic stenosis, aortic insufficiency and coronary ostial stenosis. Myocardial ischemia may be produced by acute coronary insufficiency, even in a normal heart. Hearts with intrinsic diseases are much more vulnerable than normal hearts. A variety of factors appeared to have precipitated a state of acute coronary insufficiency. These consisted of tachycardia, acute heart failure, acute hemorrhage, pulmonary embolism, dissecting aortic aneurysm, postoperative shock, and severe infection. Coronary insufficiency is usually precipitated by a physio-pathological mechanism. The clinical recognition of such a factor is essential to the accurate differentiation of acute coronary insufficiency from acute coronary artery occlusion. Where a precipitating factor for the appearance of coronary insufficiency is not detectable, the clinical episode is diagnostic of progressively advancing intrinsic cardiac disease.

The Salt Depletion Syndrome Following Mercurial Diuresis in Elderly Persons. H. L. JAFFE, A. M. MASTER, AND W. DORRANCE. *Am. J. M. Sc.*, 220: 60, July, 1950.

The dangers of intensive administration of mercurials in elderly people is emphasized. In this age group latent renal disease often exists and the loss of sodium, potassium and water may produce severe symptoms and may result in death. The commonest manifestations of salt depletion are extreme weakness, depression, a stuporous or agitated state. A clue to the condition is a rise in blood urea which should be tested at regular intervals. The blood sodium should be determined occasionally. In elderly people the usual dose of mercurial should be 1 cc. given not more often than every other day, and evidence of salt depletion searched for.

Isolated Interventricular Septal Defect with Dilatation of the Pulmonary Artery. I. G. KROOP, AND A. GRISHMAN, *Am. Heart J.*, 40: 125, July, 1950.

Isolated interventricular septal defect associated with dilatation of the pulmonary artery is presented as a clinical entity which must be differentiated from congenital lesions associated with radiographic prominence of the pulmonary artery segment, lesions including interatrial defect, patent ductus arteriosus, Eisenmenger's complex, idiopathic dilatation of the pulmonary artery, and pulmonic stenosis with post stenotic dilatation. Evidence is presented that dilatation of the pulmonary artery may be on a congenital basis, rather than on the anatomical location of the interventricular septum in relation to the pulmonary artery. Physiological data on left to right shunts are reviewed and it is shown that there is a lack of constant relation between the calculated pulmonary blood flow, pulmonary hypertension and pulmonary artery dilatation.

Toxicity of the Mucigogue, Eugenol, Administered by Stomach Tube to Dogs. F. U. LAUBER, AND F. HOLLANDER. *Gastroenterology*, 15: 481, July, 1950.

A study is reported in which dogs were given intragastric instillations of eugenol emulsions, in order to determine the toxic reactions to this compound and the order of magnitude of safe dosage. In general, body temperature was slightly depressed, and pulse rate increased, but respiratory rate was unaffected. Vomiting occurred only occasionally at a dosage level of about 2.5 gm/10 kg body weight, at the highest dosage employed (approximately 5 gm/10kg), however, its incidence was 65%. Marked motor dysfunction, primarily of the hind limbs, was observed only at this maximum dosage—and then in no more than half the experiments. Death occurred only after the highest dosage of eugenol in 2 of the 4 dogs used for the 6 experiments at this level. Thus, it would appear that a dosage of about 0.2 gm/kg (100 ml of 2% emulsion) is safe for experiments in dogs requiring orogastric administration of eugenol emulsion. Repeated administration at this dosage level (10 doses over a 3-week period) gave no indication of any cumulative effect of this substance.

Glioma of the Retina in Father and Child. J. LAVAL. *Arch. f. Ophth.* 44: 140, July, 1950.

The purpose of the report was two-fold. First, to emphasize the fact that heredity does

play an important role in glioma of the retina regardless of the usual statements in textbooks on ophthalmology that heredity is unimportant, and secondly, to demonstrate again that radiotherapy as a cure for glioma of the retina is inefficient unless the amount of retina involved is less than one sixth of the retina. Furthermore, if only one eye is affected and the other eye is normal, radiotherapy should not be given regardless of how small an area is involved; the eye should be enucleated. All survivors of glioma of the retina should be warned not to have children. The paper has photographs of the pathology and also of the fundus appearance.

Anuria Following Radiation Therapy in Leukemia. HAROLD LEAR, AND GORDON D. OPPENHEIMER. J. A. M. A. 143: 806, July, 1950.

The anuria which developed in a patient after radiation therapy for chronic lymphatic leukemia was caused by complete obstruction of both ureters with uric acid crystals. The mechanism involved is easily understood. There is an increase in the uric acid metabolism of patients suffering from leukemia. Radiotherapy causes the destruction of many white blood cells with the liberation of nucleoproteins and an increase in uric acid production. Hyperuric-acidemia, uric acid crystalluria and actual stone formation are potential dangers following radiation therapy in leukemia. By means of the case reported the authors stress the need for careful study of the urological status, uric acid metabolism and prophylactic measures to be used when roentgen therapy is given for leukemia.

Diiodohydroxyquinoline in Dermatologic Therapy. WILLIAM LEIFER, AND KARL STEINER. Arch. Dermat. & Syph., 62: 46, July, 1950.

Diiodohydroxyquinoline (Diodoquin and Floraquin) has been used for some years as an amebicide and trichomonicide, but never for cutaneous disease. Similar drugs (Quinolol, Vioform, and Sterosan) have been of value in various pyogenic and fungous infections of the skin. The authors treated 150 patients with excellent results in primary pyogenic and fungous infections, good results in secondarily infected dermatoses, and satisfactory response in certain instances of rosacea and psoriasis. The drug was well tolerated, even in inflamed and irritable dermatoses. There were 6 instances of irritation among the inflammatory dermatoses and one instance of true sensitization. No irritation or sensitization was encountered among the 66 patients with primary skin infections.

Derivatives of Butanediol-1,3. G. G. MAYER AND H. SOBOTKA. J. A. C. S., 71: 2588, July, 1950.

Several derivatives of butanediol-1,3 were prepared in connection with the synthesis of vitamin A, amongst them the monobenzyl ether, the di-trityl ether and the bis-phenyl urethan.

Hyperplastic Arteriosclerosis Versus Atherosclerosis. ELI MOSCHOWITZ, J. A. M. A., 143: 861, July, 1950.

Hyperplastic arteriosclerosis is a process that begins at birth. Evidence has been submitted that the dominant factor in its genesis is the normal intravascular tension and its increased gradient, hypertension. In this concept functional change precedes anatomic change. It is thus impossible to tell when normal aging ends and disease begins. Inasmuch as intravascular pressure cannot be escaped, it is an inevitable destiny of all animals that possess a vascular system such as the human and who live long enough. It is therefore irreversible, except under most unusual conditions. This accounts for its universality in all persons, in all climates, in all conditions of sustenance and in all eras, both ancient and modern. The process may be modified by certain factors, notably the composition of the blood, perivascular stresses and fixations and the vascular supply of the blood vessels, and in all probability by other contributing factors that remain to be determined. Its universality does not imply that clinical arteriosclerosis and anatomic arteriosclerosis are equivalent. Arteriosclerosis causes disease only when the circulation of a vital organ is impaired. Atherosclerosis cannot be considered as synonymous with arteriosclerosis since it is not primary

and lacks the consistent morphologic and/or pathogenetic background of hyperplastic arteriosclerosis. At best it is only a part or a facultative lesion of arteriosclerosis.

Effect of Cortisone and Adrenocorticotropin Therapy on Serum Proteins in Disseminated Lupus Erythematosus. MIRIAM REINER. *Proc. Exper. Biol. & Med.*, 74: 529, July, 1950.

The electrophoretic distribution of the serum proteins of 20 patients with *disseminated lupus erythematosus* showed a lowered albumin content with a considerable increase in the α_2 - as well as γ -globulin concentration. The sera of 5 patients were studied before therapy with cortisone and adrenocorticosterone (ACTH). After a clinical remission had been produced by these agents, it was found that the albumin and γ -globulin went towards normal levels, whereas the α_2 -globulin fraction remained unchanged.

The Tympanic Plexus. An Anatomic Study. SAMUEL ROSEN. *Arch. Otolaryng.*, 52: 15, July, 1950.

The author made a detailed study in one hundred cadavers of the anatomy of the tympanic plexus. This study was stimulated by the new oto-neurological concepts of the relation of the tympanic plexus and the chorda tympani nerve to the somic system in man, which is closely related to the sensation of "taste." The main trunk of the tympanic plexus is Jacobson's nerve, from which branches go to the round and oval windows, also to the Eustachian tube, the superficial petrosal nerves and the carotid plexus. The author continues research in this complex neurological aspect of otology.

Surgical Treatment of Hernia in the Aged. FRANK P. SAINBURG. *Am. J. Surg.*, 80: 60, July, 1950.

In an effort to ascertain the indications for and the results of surgical treatment of hernia in the aged, 142 unselected cases are reviewed. These cases were admitted to the ward services of Dr. Ralph Colp and Dr. John H. Garlock between 1941 and 1947. The age of sixty was arbitrarily set as a minimum for this survey; the oldest patient was ninety-eight. It was found that the wider application of elective surgery in the aged is indicated for all types of external hernias. When left to be done as an emergency procedure there was a mortality rate of 15.9 per cent, whereas in elective surgery there were no deaths. This difference is attributed to the exhaustive pre-operative medical work-ups done in the elective cases and for which there was not time in those of an emergency nature.

Post-Traumatic Aseptic Necrosis of the Distal Tibial Epiphysis. R. S. SIFFERT AND A. M. ARKIN. *J. Bone and Joint Surg.*, 32-A: 691, July, 1950.

Injuries to the growth zone of the epiphyses of long bones may result in either premature fusion with arrest of growth, or less commonly, interference with blood supply to the epiphysis and aseptic necrosis. This is the first known case reported in the literature where a crush injury to the lower tibial epiphysis resulted in aseptic necrosis. The injury was in an 11 year old boy who suffered a bimalleolar fracture of the ankle with some lateral displacement of the talus. Degenerative changes occurred in the distal tibial epiphysis, which on pathological examination at the time of ankle fusion were demonstrated to be true aseptic necrosis. It was felt that moderate injuries to the epiphyseal line may cause cessation of growth and premature fusion, but that massive crush injuries to the epiphysis itself may be responsible for aseptic necrosis as occurred in this case.

Response of Gastric Mucous Barrier in Pouch Dogs to Repeated Topical Application of Eugenol. H. A. SOBER, F. HOLLANDER, AND B. P. SONNENBLICK. *Am. J. Physiol.*, 162: 120, July, 1950.

Successive applications of eugenol to the mucosa of Heidenhain pouches, at intervals of about 3 hours, resulted in a progressive diminution in amount of mucus secreted, with a gradual increase in the quantity of a clear, free-flowing, sero-sanguinous fluid mixed with the viscons material. The proportion of the non-viscous component became considerable

only after 3 or 4 such applications, and by the fifth or sixth, the material was entirely serous and virtually free of true mucus. From this, it is evident that the mucus-secreting function of the dog's pouch is seriously impaired by 3 to 4 treatments with eugenol and that no more than 5 or 6 such applications are required for its fatigue or complete exhaustion. Function is quickly restored, for 36 hours after the end of such a prolonged experiment the mucosa gives appreciable evidence of renewed mucus-secreting activity. Recovery is not extensive, however, for the secretion now assumes a sero-sanguinous character much sooner. After 3 to 5 months, the mucus-secretory function had been restored almost to its original state.

Thus, a set of experimental conditions has been defined for the exhaustion of mucus-secreting activity in canine gastric pouches. This process includes a loss not only of cellular function but also of cells themselves, from which it may be inferred that the mucous barrier has been seriously impaired and perhaps even completely destroyed.

The General Hospital in Community Planning for the Aged. MARTIN R. STEINBERG. Geriatrics, Vol. 5, No. 4: 231, July-August, 1950.

The modern general hospital is a costly collection of facilities and personnel which does not fully justify its existence, the author contends, unless it strives to serve the community in relation to all of its health problems, including care of the aged. Prejudices of staff and personnel against working with the aged (who are viewed by them as difficult patients) can be overcome through re-education, and closer liaison must be established with old age institutions, if the general hospital is to assume its proper burden in this largely-neglected field. The article cites examples of good beginnings in both directions at Mount Sinai Hospital.

Direct Reorientation of Behavior Patterns in Deep Narcosis (Narcoplexia). R. M. BRICKNER, R. T. PORTER, W. S. HOMER, AND J. J. HICKS. Arch. Neurol. & Psychiat., 64: 165, August, 1950.

A psychotherapeutic method is described which utilizes directly certain neurophysiologic factors. Amobarbital sodium (amytal® sodium) is administered intravenously, and a series of subsequent steps is systematically employed. The drug induces a certain physiologic state; this state is discussed; we believe it can be understood to a certain degree. When the brain is in that state, specific psychologic impacts often can be made with unusual directness. Frequently this results in unusually rapid psychologic changes. Usually these psychologic changes appear to be unlike those of hypnosis. During the procedure patients frequently reject material which is given them and seem to be prompted to do quick, direct work of their own on the solution of their problems. Sometimes this work has an original quality. Moreover, psychologic changes, once made, are usually lasting. Occasionally patients do respond to the material given them as though to direct suggestion, but under these conditions also the changes are lasting. The reinforcement many patients obtain during postnarcosis waking therapy may help in establishing the permanence of changes made during narcosis. Responses suggestive of abreaction occur occasionally. Patients with at least one year of follow-up observation showed the following therapeutic results: Of 12 patients with psychoneuroses, all but 1 showed improvement graded as better than moderate, and more than half showed improvement graded as marked or very marked. Of 11 patients with borderline states, 4 showed improvement graded as better than moderate, and 3 showed improvement graded as marked or very marked. On the whole, the bulk of the intensive psychotherapeutic work is completed under narcosis. Most psychoneurotic patients who have responded well under narcosis require virtually no thorough waking therapy. A greater amount of waking therapy is sometimes needed with patients who have responded only fairly well, especially if they are in the borderline group. The method has the following advantages:

1. It is applicable to cases which present extremely difficult psychotherapeutic problems.
2. The major and basic portion of intensive psychotherapy is usually completed in about two months.

3. Resistance is rarely encountered either during the narcosis part of treatment or during subsequent follow-up work.

4. Factors inherent in the process make possible a considerable degree of specificity and accuracy in following a patient's course, in evaluating the effects of therapy as it progresses and in planning steps as treatment advances.

Studies in Pancreatic Function. II—A Statistical Study of Pancreatic Secretion Following Secretin in Patients Without Pancreatic Disease. D. A. DREILING, AND F. HOLLANDER. *Gastroenterology*, 15: 620, August, 1950.

A series of 172 patients without pancreatic disease was studied. Of these, 81 constitute a homogeneous group, all members of which were tested with a new preparation of secretin (Wyeth). The remaining 91 patients represent the heterogeneous series which was previously studied with Astra secretins of different ages, and with earlier Wyeth preparations. The test procedures for both studies was exactly the same as that previously described by the authors; the stimulating dose was 1.0 unit of secretin per kilogram and the collection period was 80 minutes. A statistical analysis of the volume, bicarbonate, and amylase data for both series is presented. Norms have been established. A study of the data has yielded evidence for the use of an 80-minute collection period and for the inclusion of enzyme determinations in the clinical application of the procedure. Body weight adjustment of the values for total volume of secretion and total quantity of amylase results in a marked decrease in the scatter of the data, and therefore, narrowing of the range of normalcy. For this reason, volume and enzyme data should be reduced to a per kilogram basis.

The Variability of the Electrocardiogram in Congenital Tricuspid Atresia. I. G. KROOP AND A. GRISHMAN. *J. Pediat.*, 37: 231, August, 1950.

Left axis deviation may be absent in some cases of tricuspid atresia and its absence should not rule out the diagnosis. Age and the presence or absence of transposition of the great vessels are not determining factors. The factor which determines the left axis deviation is the positivity in aVL and the negativity in aVF. Despite the presence of left ventricular hypertrophy and a hypoplastic right ventricle in tricuspid atresia, definite diagnostic electrocardiographic evidence of left ventricular hypertrophy as it is seen in children and adults is absent. The enlarged right atrium by rotating the large left ventricle may strongly effect the potential distribution to the chest.

Experimental Evaluation of Recording to Alternate Ears as an aid in Localization. M. A. LENNOX, AND J. A. EPSTEIN. *Electroenceph. & Clin. Neurophysiol.*, 2: 333, August, 1950.

It was possible to follow the changes in the electroencephalogram during a protracted period in a group of 29 dogs in whom the middle cerebral artery had been clipped close to its origin. A slight variation in the location of the clip was unavoidable but useful in that the size of the resulting infarcts differed. Massive lesions included the cortex in the fronto-temporo-parietal region, the striatum, the internal capsule and the anterior portions of the thalamus and, rarely, the hypothalamus. The majority of lesions were confined to the internal capsule and to the caudate nucleus. The clinical syndrome consisted of a contralateral spastic hemiparesis with the loss of the placing reaction and of position sense. Forced circling movements occurred towards the side of the lesion, persisting even after blindfolding the animal. The changes in the electroencephalogram varied with the size of the lesion. In the scalp to ear records, slow frequencies were most conspicuous over the involved hemisphere in all types of recordings and were most prominent in recording to the contralateral ear. In the scalp to scalp records, flattening was evident over the frontal and temporal regions and slow frequencies were conspicuous posteriorly. Flattening was found over the entire hemisphere only in the most massive lesions and then in both types of recordings. The scalp to scalp records tended to become more symmetrical after two to three weeks, the flat tracings being replaced at times by high voltage slow frequencies. The abnormalities in the

scalp to ear records tended to persist for the duration of the experiment. Flat records were obtained in the electrocorticogram overlying the area of infarction, and high voltage slow waves were found in the peripheral zone. Using the multipolar needle electrodes, an unusually low voltage to flat records was obtained from the depths of the lesion. A fairly constant change was the loss of the high voltage 10-12 per sec. spindles from the fronto-central scalp electrodes and from electrodes placed on the sigmoid gyri. The sleep records were far superior to the waking records as a diagnostic aid, the latter being of value only during the first post-operative week.

Hysteroscopy and Hysterosalpingography: Analysis of 2,500 Cases with Special Emphasis on Technic and Safety of the Procedure is Presented. R. H. MARSHAK, C. S. POOLE, AND M. A. GOLDGERGER, Surg., Gynec., & Obstet., 91: 182, August, 1950.

Optimal time for performance is one week after cessation of menses. A preliminary x-ray of the abdomen is taken and the patient placed in the lithotomy position. With a fiber, bivalved speculum, the cervix is exposed; it is painted with antiseptic solution. After preliminary sounding of the uterus, iodized material is introduced through a cannula which may be attached to a manometer. The material is injected slowly and gently. In hysteroscopy, 1 cc. dye is injected and a film taken. Fractional amounts of opaque material, up to 3 or 4 cc., are introduced and films taken at each injection. The dye is injected under low pressure; if obstruction is encountered, injection is discontinued. In sterility cases, larger amounts of dye (up to 6 cc.) must be used. In uterosalpingography, injection of lipiodol is discontinued when obstruction to flow of the dye at 200 mm. Hg is encountered; however, if a water-soluble agent is used pressures up to 250 mm. Hg may be utilized. If films do not reveal lipiodol in the peritoneal cavity, a 24 hour film may be taken for aid in differentiation of organic and functional tubal obstruction. With use of water-soluble mediums, the dye should reach the peritoneal cavity, since a delayed film cannot be taken because of rapid absorbability. With the use of lipiodol, the 24 hour film may aid differentiation of spasm and organic closure of the tubes. Complications due to contrast mediums are pain, peritonitis, endometritis, allergic phenomena and emboli. None are serious or cause permanent damage. Except for moderate pain, the quickly absorbing mediums are harmless. Rarely, lipiodol may cause embolization and formation of a granuloma in a previously diseased tube. Complications due to the procedure are hemorrhage, exacerbation of chronic pelvic inflammatory disease, perforation of the uterus, shock, visualization of the uterine vascular structure and introduction of radio-opaque medium into a pregnant uterus. In this series there were two cases of hemorrhage, neither of which were serious. Pelvic inflammatory disease was reactivated seven times and the uterus perforated once. Hysterosalpingography did not adversely affect any pregnancy. The water-soluble mediums proved satisfactory for uterosalpingography.

Meckel's Diverticulum Producing Chronic Intestinal Obstruction. R. H. MARSHAK, AND A. I. FRIEDMAN, Gastroenterology, 15: 754, August, 1950.

Most cases of intestinal obstruction from Meckel's diverticulum develop acutely. The following patient had a long history with frequent, intermittent attacks of obstruction in the distal ileum that was secondary to one of the largest examples at Meckel's diverticulum we have observed.

A male physician, aged 36 years, was seen by Doctor B. B. Crohn with a chief complaint of abdominal pain of 18 years' duration. In this period frequent attacks of fever, generalized abdominal pain and vomiting had occurred, during one of which, an appendectomy was performed without relief. Since 1945 the attacks were associated with diarrhea. Repeated radiographs of the gastrointestinal tract were not diagnostic until 1949. When a barium meal examination revealed considerable dilatation of the distal jejunum and proximal ileum. A peculiar pear-sized mass 8 cm. in diameter containing barium was felt in the pelvis. An exploratory laparotomy performed by Doctor John Garlock revealed a huge Meckel's diverticulum $2\frac{1}{2}$ feet from the ileocecal valve. The mid-ileum was distended to ten times its

normal size with a markedly thickened wall. The diverticulum measured 9 x 10 cm. The mouth of the sac was 8 mm. in diameter.

The Normal Blood Pressure Range and its Clinical Implications. A. M. MASTER, L. I. DUBLIN, AND H. H. MARKS. J. A. M. A., 143: 1464, August, 1950.

Hypertension is a common diagnosis in medical practice and is usually considered to bear a serious connotation. Yet the levels which constitute abnormally high blood pressure at various ages have not been accurately determined. Since blood pressure readings as high or higher than those widely accepted as the upper limits of normal are so frequently encountered, particularly in persons over 40 years of age, it is desirable that the range of normal blood pressure should be reconsidered. Tables are presented showing the normal range of systolic and diastolic blood pressures with limits of hypotension and hypertension on the basis of examination of 74,000 persons. The possible sphere of application of the work presented in this paper is wide in clinical, industrial, and military medicine as well as in insurance and research.

Aerosol Streptomycin Treatment of Advanced Pulmonary Tuberculosis in Children. J. B. MILLER, H. A. ABRAMSON, AND B. RATNER. Am. J. Dis. Child., 80: 207, August, 1950.

The factors which seem most important in diminishing streptomycin activity in human pulmonary tuberculosis are the relatively low concentrations obtained in the lungs and tuberculous cavities by intramuscular injection of the drug, the insolubility of aqueous streptomycin in the highly lipid caseous exudate and the inactivation of streptomycin by the acid pH of caseous material. Streptomycin was administered into the lungs as an aerosol in concentrated solution and in large doses, dissolved in a special diluent containing an alkaline buffer and a stable detergent. A critical examination of conventional methods led to the development of new techniques to increase the efficiency of the method and to adapt it to infants and children. Twelve children with various forms of pulmonary tuberculosis, at least 5 of whom had poor prognoses were treated. The disease responded in all but 3 children who had atelectatic lesions, by apparent healing. The most rapid response occurred in those children with the greatest amount of infiltration, consolidation and cavitation. No significant toxicity or sensitivity occurred in the patients or personnel.

Early Observations on the Mechanism of Auricular Fibrillation. B. S. OPPENHEIMER, AND ADELE O. FRIEDMAN. Cardiologia, 16: 308, August, 1950.

In view of the recent evidence against Lewis' theory of circus movements as the basis of auricular fibrillation, it seemed of interest to publish old experiments performed on dogs in 1910 designed to test Engelmann's concept of the mechanism of auricular fibrillation. This is the theory of the multifocal ("polyfocal" or "polytopic") origin of fibrillation. From these old experiments it was concluded that it was the rate or frequency of effective stimulation of the auricle, whether at a single focus or at multiple foci, whether at the sino-auricular node or at some ectopic point, whether at regular or irregular intervals, that was the one important factor in precipitating auricular fibrillation. Engelmann's theory of the multifocal origin of auricular fibrillation was not confirmed.

N-Ethyl-O-Crotono-Toluide (Eurax) as an Antipruritic. S. M. PECK, AND T. MICHELFELDER. New York State J. Med., 50: 1934, August, 1950.

N-ethyl-o-crotono-toluide in a water soluble ointment base was investigated for its antipruritic properties in various dermatologic conditions. The antipruritic effect was quite satisfactory and this preparation was found to have a low sensitizing index as well as an absence of toxicity. It was tried in about 400 individuals with various dermatologic conditions.

A Case of Diagnosis (Pemphigus)? S. M. PECK, Arch. Derm. & Syph., 62: 349, August, 1950. J. V., a woman aged 48, was studied at Mount Sinai Hospital from January to April

1948 because of alopecia areata, dermatitis of the face and ears and a vesicular eruption of the mucous membranes. The cutaneous eruption was of five years' duration and has cleared up under treatment. The mucous membrane lesions are of one year's duration and persist. Impressions during her previous admission were as follows: 1. Contact dermatitis in which sensitization played a minor role was present. 2. The causative factor reached the skin through the blood stream. 3. The oral lesions and flare following the use of antiseptics pointed either to an infection (virus or bacterial) or to an allergy of obscure type (food?). 4. A psychosomatic component was present but did not predominate. While in the hospital, the patient failed to respond to various forms of local therapy or to elimination diets. The administration of penicillin had no effect. Local application of iodochlorohydroxyquinoline (vioform[®]), ointment 3 per cent, helped the cutaneous eruption. The superficial ulcers of the tongue and gums failed to respond to any therapy. The Wasserman reaction of the blood was negative. A blood count showed 12.3 Gm. of hemoglobin and 5,700 white blood cells, with a normal differential count. The erythrocyte sedimentation rate was 12 mm. per hour. Biopsy of a specimen from a vulvar lesion, performed because of pruritus, showed leukoplakia. A roentgenogram of the chest revealed mediastinal hernia. The results of urinalysis were normal. The urea nitrogen was 13 mg. per hundred cubic centimeters. A patch test with 10 per cent nickel sulfate gave positive reactions on one occasion. Since discharge from the hospital in April 1948, the patient has been followed in the outpatient department and has been studied by the medical, orthopedic, nose and throat, ophthalmologic and psychiatric services. At the nose and throat service it was believed that the patient might have pemphigus because of the lesions on the tongue, gums tonsillar pillars, epiglottis and larynx. Since Nov. 1, 1948, the patient has been taking carbarsone, 250 mg. daily for three days followed by a three day rest, and also therapeutic doses of vitamin A, the B complex and ascorbic acid, with no effect on the lesions of the mucous membranes.

Therapy of Ragweed Hay Fever with Electrophoretically Isolated Fractions (Artefolin and Trifidin). Preliminary Report. H. A. ABRAMSON, M. LOEBL, H. H. GETTNER, AND B. SKLAROWSKY. *Ann Allergy*, 8: 594, September-October, 1950.

With the cooperation of a group of allergists in various parts of the United States, electrophoretically purified colorless ragweed antigen (Trifidin and Artefolin) were used in the therapy of 56 cases of hay fever and asthma. A new preparative method for obtaining these antigens with simplified electrophoretic comprises the control of heat convection, by using liquids of high coefficients of viscosity and low conductance, making the technique practical at room temperature. Because of losses encountered in purification only small doses of pollen antigen were available for therapy. It was found, on the basis of this small series, that good results were obtained in 70 per cent of the patients treated. It is believed that (a) in freshly prepared ragweed extracts, not subjected to elaborate laboratory procedures which lead to the molecular aggregation, the largest molecule of antigenic significance in the production of and therapy of ragweed pollen hay fever is of the order 5,000 molecular weight, and (b) it is this molecule that is responsible for the favorable results reported here in the therapy of ragweed hay fever and asthma. This molecule may, in higher doses than that reported here, provide better protection to the patient than the high doses of crude mixtures of ragweed pollen extracts.

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CONTENTS

	PAGE
FOREWORD	iii
MEDICINE AND SOCIETY: AN HISTORICAL PERSPECTIVE. <i>Richard H. Shryock, Ph.D.</i>	699
MEDICINE AND SOCIETY: THE BIOLOGICAL FOUNDATIONS. <i>Paul Weiss, Ph.D., M.D. (Hon.)</i>	716
HEALTH, MEDICINE, AND ECONOMIC WELFARE. <i>Eli Ginzberg, Ph.D.</i> ...	734
MEDICINE AND THE COMMUNITY: THE ROLE OF THE VOLUNTARY HOSPITAL IN COMMUNITY MEDICAL CARE. <i>George Bachr, M.D.</i>	744
A CENTURY OF MILITARY MEDICINE. <i>Major General George E. Armstrong</i>	754
PUBLIC HEALTH, 1852-1952. <i>Leonard A. Scheele, M.D.</i>	764
MEDICINE AND SOCIETY: THE ROLE OF PSYCHIATRY. <i>William C. Menninger, M.D.</i>	790
MEDICINE AND SOCIETY: IMPLICATIONS IN THE ATOMIC AGE. <i>Austin M. Brues, M.D.</i>	812
AN INTEGRATION. <i>Alan Gregg, M.D.</i>	821
INDEX TO VOLUME XIX.....	831

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FOREWORD

The celebration of the centennial of the founding of THE MOUNT SINAI HOSPITAL was originally to include a series of lectures. The plan was to divide the program into scientific presentations to the medical profession, and lectures to a wider group of the laity interested in the Hospital's achievements. However, after careful deliberation the Committee decided that the occasion would best be served both for physicians and laymen if the broad aspects of medicine as an intrinsic part of the community were discussed. The practice of medicine derives its directions not only from the natural sciences. Scientific medicine is not the sole custodian of the health of the individual or of the people as a whole. Medicine is an agency of society and thrives in the climate of the national and international community. Medicine is also a force which influences the life of society and contributes to its advancement. The impact of society on medicine and society's reaction to the progress of medicine in the past century was, therefore, chosen as the topic for this symposium.

FOR: *The Symposium Committee.*

M. RALPH KAUFMAN, M.D., GEORGE BAEHR, M.D.

PAUL KLEMPERER, M.D.

MEDICINE AND SOCIETY: AN HISTORICAL PERSPECTIVE

RICHARD H. SHRYOCK, PH.D.*

The relations between Medicine and Society have been pondered through the centuries by both physicians and laymen from varying perspectives depending upon time and place as well as upon the individuals involved. Although much the same thing can be said of all arts and professions, an unusual degree of attention has been accorded Medicine because of the universality and the peculiarly vital nature of its social implications. For these same reasons, the social relations of Medicine were often quite different from those of other sciences; so that the history of Medicine is in a sense more than a chapter in the history of Science (1).

Early discussions of Medicine in relation to Society were usually of a selective, casual and even fragmentary nature, dealing with this or that aspect of the totality; but in recent centuries more comprehensive analyses have been attempted. I note at random, for example, the publication of a Paris thesis in 1821 on "The Relations of Medicine to Society in General" (2). The subject has obviously become more complex over the past century, what with the acceleration of change in both Medicine and in Society, and now attracts the attention of social scientists and historians as well as of physicians.

One need only recall the overlapping meanings of such terms as preventive medicine, public health, social medicine, medical sociology, medical care, and so on, in order to sense how complex indeed is the subject before us. The historian, whose function is to provide perspective on this many-sided story, must use some scheme of analysis in the process—some breakdown of topics—and should make clear the definitions or meanings employed. The word "Medicine" will be used here in a most comprehensive sense, to include that combination of arts and sciences whose purposes are the promotion of health, and the prevention, cure, or amelioration of illness. The word will also cover the professions which pursue these sciences or practice these arts. As for the term "Society," I would make only a negative observation. The very dichotomy of the phrase "Medicine and Society" implies that the first of these, as part, is distinct from the second, as the whole. Hence the word "Society," as here employed, means the entire culture or civilization of any given time and place *other than* Medicine. Or we may say that Society is the total human environment in which Medicine, as an entity, moves and has its being.

The distinction here is by no means an artificial one. The historian observes that Medicine has always responded to its social environment, but that it has also been guided by a sort of internal logic of its own. The latter tendency is plainly characteristic of medical science and is also true in some measure of the medical professions as self-conscious guilds. Scholars have often erred in em-

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phasizing one of these trends at the expense of the other. General historians have viewed Medicine chiefly as a reflection of the surrounding culture, while medical historians presented it almost as if it had evolved within a social vacuum. A more balanced method is to distinguish the external from the internal circumstances and then to interpret that constant interplay between them which has actually occurred throughout the past. The same procedure, it may be added, can be applied to the history and sociology of any or all of the scientific fields.

One can hardly, in a single paper, survey the interplay between Medicine and Society over all space and time. In order to bring this discussion within feasible limits, therefore, I shall focus on a subject which is relatively familiar and also appropriate for this occasion; that is, the American story during the last hundred years.

* * *

The American society of the 1840's and 1850's was still a predominantly agrarian one, but the industrial revolution and urbanization were well under way. The basic phenomena of illness which Society presented to Medicine therefore included both those long common to rural areas, and certain relatively new developments associated with urban centers. Many data, of course, were common to both settings.

Just which of these phenomena were considered significant by physicians, and the manner in which they handled them, depended in part on public attitudes, in part on the nature of medical science and related disciplines. The great attention accorded epidemic diseases certainly reflected public fear as well as the popular assumption that it should be easier to avoid unusual outbreaks than it was to check illnesses which—like the poor—were always present. Each major disease had its own social psychology. Yellow fever inspired fear and flight; tuberculosis, fatalism and even a suggestion of romance (3). Physicians not only participated in these reactions as citizens, but were also conditioned in their capacity as experts by public feeling. These pressures were greatest in cities for obvious reasons, and in the cities were located the leaders of professional opinion. In this setting, Society influenced Medicine.

Although medical interest was focused at intervals on epidemics, it was also being directed by the 1840's toward certain widespread, endemic forms of illness. The average practitioner, in dealing with various fevers and fluxes, was still guided by a scientific tradition which had come down to him from classical Greece via the eighteenth century. He was still concerned with his patient's "constitution," thought more of the general state of the latter's "system" than he did about an exact diagnosis, and employed bleeding and other depletion procedures intended to rid the body of noxious humors.

Although we are once more, today, inclined to urge physicians to "treat the whole man," it should not be forgotten that this could have sorry results when the method was an unfortunate one. It is impossible to measure the damage once done in Society by excessive bleedings and purgings, but able contemporary observers—both lay and medical—thought it was considerable (4). A popular revolt against these practices was under way by the 1840's, expressing itself in

a growing support of such professional sects as homeopathy and Thomsonianism, and this revolt was one factor in the gradual abandonment of heroic practice thereafter by the regular guild (5a, b). Here, again, Society had its impact on Medicine.

Another factor in the revolt against heroic practice was the changing attitude of medical scientists, as distinct from the rank and file of practitioners. We are all familiar with the revolution in medical thought which occurred during the first three or four decades of the nineteenth century, and which was associated especially with the so-called Paris school. For complex reasons which cannot be reviewed here, the internal logic of medicine led—somewhat independently of social circumstances—to a changed concept of the nature of disease (6). Traditional humoral theories were replaced by a localized, structural pathology associated with the idea of disease specificity. This idea, although by no means new, had never dominated medical thinking before. It greatly stimulated research. First came the effort to identify particular diseases through a correlation of pathologic and clinical data; and, once this was done, a further effort was made to discover specific causes, cures, and means of prevention.

The implications for general practice were plain enough. If pathology was specific rather than general, localized rather than diffused, treatments also must be specific. Procedures long viewed as good for everything were now condemned as good for nothing. Although science had not yet found specific remedies to replace these, honest medical nihilism was deemed better than false promises. Oliver Wendell Holmes, trained in Paris, went even further than the sectarians in condemning excessive medication. By 1850, medical scientists actually wished to protect Society from the effects of outdated medical practice. Nearly fifty years later, Osler still felt it necessary to present this view in the first edition of his famous text—a fact which provides some indication of the lag between research and practice.

The localized, specific pathology had at first a more positive effect upon surgery than it did upon internal medicine. The old theories had restricted surgery to superficial emergencies, since one could hardly operate upon the blood or other humors, but the new emphasis on localization moved surgery from the periphery to the very center of practice. There followed a search for such improved procedures as anesthesia and antisepsis, which were in this sense effects rather than causes of the new surgery (7). In due time, the use of the concept of specificity led also to striking discoveries concerning the etiology of infectious diseases, and these in turn to real accomplishments in prevention and even in cure. The pathology of the 1850's was followed by the bacteriology of the '80's, and the latter by the preventive medicine of the early 1900's.

The main drive in this sequence was internal to Medicine, but its course was eased by certain developments in Society. The first of these was a negative one; that is, the old moral tabus against human dissection declined early in the century, and this facilitated the work in pathologic anatomy and in surgery. Unfortunately, opposition lingered longest in the English-speaking lands, where it was enlivened by grave robbing and doctors' riots. Such disturbances occurred

in the United States well after the first Massachusetts anatomy act of 1833, and popular distaste for autopsies continued to handicap medical scientists throughout the century. Equalitarian sentiments, as well as moral convictions, made things difficult for investigators in this country. Certainly there was no inclination to make the bodies of the poor easily available in the European manner. Similar feeling protected ward patients from the inquisitive glances of medical students—a situation which led universities to set up their own hospitals after 1875 in order to provide students with clinical teaching and experience. Jacksonian democracy protected the rights of the common man, living or dead.

While such social outlooks in the States seemed inimical to medical science, certain cultural trends in Europe were of great value to Medicine. Philosophic empiricism, materialism, and positivism alike encouraged original work in the natural sciences after 1800. The idea of “progress” permeated all these outlooks and proved a most stimulating one. A distinction arose between basic and applied science which may or may not have been necessary; but in any case science encouraged technology at certain points, and the latter in turn sometimes stimulated basic investigations (8). These trends influenced medical science in two ways. First, they encouraged systematic, empirical investigations, and the abandonment of the sort of speculation which had persisted—with such a leader as Benjamin Rush in the United States—into the early 1800’s. The story of the *Idéologues* in Paris well illustrates this theme (9).

In the second place, mathematics, the natural sciences, and technology became directly helpful to medical science—thus repaying the debt which these fields had long owed to physicians. Mathematicians developed statistics and the calculus of probabilities, and pointed out that these tools might be employed in medical studies. Clinical statistics, which began to be used systematically by 1830, played a part in discrediting heroic practice, while vital statistics became essential to epidemiology and therefore to the public health movement (10). The contributions of the physical sciences to the medical, from about 1775 to 1875, need hardly be repeated here—one only has to recall, for example, the work of certain chemists from Lavoisier to Wöhler. Nor is technology to be overlooked, as in the improvements of lenses and the consequent appearance of the achromatic microscope by 1830.

A general enthusiasm for research was becoming institutionalized, after 1800, in the continental universities, and, in the case of medical science, this spirit was carried over into teaching hospitals. Neither universities nor hospitals had originally been set up for this purpose; hence their transformation was of major importance to Medicine. Also of service to the latter was the increase in the size of hospitals, which provided an amount of “material” for clinical and pathologic studies which was lacking in ordinary practice. Without such material, much research in Medicine would have been impossible. Thus medical progress depended, far more than did that in the physical sciences, on the social phenomenon of urban growth.

One must admit that enthusiasm for research made little headway in English universities before 1875, though it did invade the London hospital schools. And

when one again turns his glance to the United States, it is at once apparent that here the research spirit was inhibited everywhere by a pervasive, "practical" indifference to basic science. Why should this be supported if it held out no promise of immediate utility? Technology flourished, but under the circumstances did little to stimulate "pure science." And no science was "purer" in this sense, during the years 1800 to 1875, than was pathologic anatomy—the medical field *par excellence* of that day. Very few American physicians had what could be called research careers prior to the latter date, and no cities became research centers before 1890. Modern Medicine would never have evolved had it been left to this country, or, at best, it would have developed much more slowly (11).

One can hardly blame American physicians of that era for contributing so little to basic science. They were the products of the Society in which they happened to dwell. Their livelihood depended, as in all capitalistic societies, on competitive, solo practice; and success in this determined appointments to medical faculties. Hence the medical professor was by definition a busy practitioner who had little time for investigations. Comte observed that this situation was as bad for medical science as it would have been for astronomy had that field been dependent upon the observations of sea captains. But in Europe there was at least some prestige in research, while in the States even this encouragement was lacking. The difficulties of American medical faculties were increased by the commercialization of medical education and a decline in the public status of the profession—trends which grew out of the whole state of American society in the mid-century period.

Toqueville, in his penetrating analysis of American culture in the 1830's, suggested that basic science would have been promoted here had it not been so easily available in Europe. Although I would doubt this, it is certainly true that medical science was promptly imported, as in translations from the French until about 1870 and from the German thereafter. Various medical professors also "edited" English works, or, as Holmes put it, placed "British portraits of disease in American frames." There were, of course, instances of originality. Samuel Gross produced in 1839 what was probably the first real text in pathology in any language (12). Beaumont did basic work in physiology, as did Drake in geo-medicine and Leidy in parasitology. It is obvious, too, that American surgery made real advances, as in dentistry and in the anesthesia introduced by dentists. These latter achievements well expressed the native bent for the "practical."

The activities of American professors in editing European works, and in contributing incidental articles to journals, probably concealed in some degree the lack of basic studies. A somewhat similar effect resulted from the cultivation of a vague philosophic idealism, derived from the German *Naturphilosophie* and from Anglo-American transcendentalism, which enabled medical professors to hide their lack of originality behind a dignified metaphysical facade. It was somewhat easier to orate on Nature and on Nature's God than it was to perform autopsies.

All this blended nicely into the religious enthusiasms of the mid-century. Occasionally, these enthusiasms engendered some opposition to science—as in voicing a suspicion that French medicine was materialistic. Silliman once wrote Beaumont, *re* certain difficulties in the latter's work that "the laws of the Creator are often incomprehensible equally in His nature and in His works." One gathers that there was not much which Beaumont could do about it. But there was little open theological opposition to Medicine, and the latter field suffered chiefly by indirection, in that a large portion of able professional students preferred divinity to the scientific fields until well after 1850 (13).

* * *

Whatever its origins, the latest medical science was available in the United States throughout the nineteenth century. It were well, therefore, to return here to the other side of our subject: the influences exerted by this science upon Society. It is impossible to measure what one might term the incidental results of the prevailing, solo practice of medicine during the last half of the century. As this became less heroic, whether in the hands of regulars or sectarians, it presumably did less damage. And the use of certain drugs—quinine, opiates—had curative or ameliorative values. Major surgery made great progress toward the end of the century, and—as in the classic case of appendicitis—began to save lives. The crude death rate was declining slowly, and the average life expectancy at birth increasing; but one can hardly disentangle the medical factor in these trends from those resulting from increasing real wages, higher standards of living, improved personal hygiene, and the like.

The rank and file of physicians could claim little credit for such declines in morbidity as resulted from improvements in the general manner of living. Since time immemorial, practitioners had been chiefly concerned with just one stage in the sequence of illness; that is, with cures. Society rewarded them only in this connection, and not for promoting health, preventing illness, or rehabilitating the victims thereof. It is true that the good family doctor of 1850 or 1875, especially the rural doctor, knew his patients well. Hence he was sometimes aware of non-somatic factors in disease—of personality and of social circumstances—and doubtless gave advice in this connection. Although this was done on the common-sense level, authority lent force to his guidance.

Unfortunately, the very progress made in pathology encouraged a purely somatic approach in medical science. Attention began to be focused exclusively on physical agents in disease causation and on structural changes in disease processes. Bacteriology pushed this trend further after 1890. The patient ceased to be viewed as a person and was envisaged rather as a "case." It was the disease entity which was interesting. Meantime, the expansion of the medical school curriculum—under the pressure of increasing knowledge and specialization—discouraged the old apprenticeship in medical education. Students, in consequence, ceased to see patients in their normal, home environments, and even the common-sense appreciation of social factors disappeared from view.

Such factors were always there—familial tensions, occupational dangers, poor living conditions—but medical science ignored them because they could not be

fitted into the internal logic of the time. Certain lay leaders sensed this neglect and organized their own programs for preserving health. There were, for example, the mid-century hygiene cults which demanded just what physicians usually ignored; that is, the promotion of positive well being and the prevention of disease. Such was the crusade of Sylvester Graham, who advocated bathing, better diets, dress reform, exercise, and buoyant living. His zeal for whole-grain cereals anticipated later interests in vitamins and "roughage," and he is unconsciously recalled today in references to "Graham bread" or "Graham crackers." We should not scoff at the Graham boarding houses or the "Ladies' Physiological Reform Societies" which arose in his wake, for they were seeking the very values which physicians overlooked (14).

It is true that individual doctors had long advocated personal hygiene, and the popular health reformers borrowed much from older medical authorities. (The one false note in Graham's appeals—his naive notions on sex hygiene—was taken over from such earlier medical lights as Beddoes and Tissot.) But the undoubted improvements in living standards and personal habits after 1850, and such effects as these had on morbidity over the ensuing half century, can be largely ascribed to economic trends and lay activities.

* * *

At first glance, the professional record in *public* hygiene, 1850–1900, seems scarcely more impressive than that in personal hygiene. Operating in a Society which rewarded them only for curing individuals, the majority of doctors gave little heed to preventive measures in general or to mass controls in particular. No doubt some of them were in the medical game for what it could bring, and they were often accused of holding a vested interest in the perpetuation of illness. Most doctors, nevertheless, were not mere business men: they could not escape entirely the tradition of public service which came down from medieval days. They were ever reminded of this by patients, who demanded more of them than of ordinary tradesmen. They were called upon at any hour, but were paid only when it was convenient. They were expected to serve the poor without compensation. And in times of crisis, they were looked to for public guidance and must not desert their posts.

Prominent physicians, assured of their position, gave more heed to the traditions of the guild than could the rank and file. It was such men who had organized the early medical societies, 1750 to 1850, which strove to regulate the relations of doctors to Society and to one another. And such men often recognized an obligation to be concerned with the state of the public health.

During most major epidemics, from the smallpox of 1721 to the cholera of the 1850's, public officials had called upon medical groups for guidance. The latter provided this in terms of prevailing theory, which in the eighteenth century had emphasized contagion. Hence most of the health regulations of that era had related to notification and isolation. But it should not be forgotten that the introduction of the first definite procedure in preventive medicine—inoculation and later vaccination against smallpox—owed much to physicians from Boyleston to Waterhouse. Throughout the nineteenth century, vaccination—

usually practiced by physicians limited the ravages of that disease; and this was as positive a contribution to human welfare as were any of the products of the physical sciences.

There were of course various ways in which physicians could protect the people's health, other than by what were usually termed "public health" measures. The very existence of competitive, solo practice on a large scale was itself a social phenomenon, and it was generally assumed that the profession could best serve Society through this system. For this reason, public authorities had long taken an interest in such matters as licensing, the regulation of fees, and malpractice. Unfortunately, public doubts about regular medicine in the 1850 period led to lower standards in licensing, which was in effect turned over to the medical schools. And since many of the latter were mediocre or worse, access to the profession became almost a free-for-all. It is no wonder that confidence in ordinary medical practice declined even further.

This lack of confidence helps to explain why there was so little concern about the medical care of the masses. If medical science was none too effective, and the medical profession none too impressive, why worry even if the poor *were* neglected? There had been more concern about this during the preceding century, when traditional regard for medical learning had combined with humanitarian zeal in advocating some systematic medical care for the working classes. In England, for example, the "poor-law" system had long provided free, local service to the poor, although this was essentially charity practice. Skilled workers, seeking to avoid charity, had met medical costs by prepayments to voluntary, beneficial societies, but these rarely served the poorest classes. Convinced that the latter should also be protected, some reformers urged that this principle be imposed on the entire "labouring class" through some system of compulsory, state health insurance. Premiums could be paid by both employers and employees and be supplemented if necessary by taxation. Such a program was actually applied to certain groups in England after 1750, and its adoption in this country in the Marine Hospital Service about 1800 is well known (15).

Yet little was said thereafter about compulsory health insurance until the German legislation of the 1880's, and there was a great silence on the subject in the United States throughout the century. One might explain this by a lack of need among the poor—wages were higher in America—or by the general acceptance of *laissez faire* principles in this country. It need hardly be added that actuarial calculations had not yet reached a point where they could well have been applied to the health risks of a large population. That the usual fee-for-service system of payment did not fit everyone's needs, however, is suggested by the sick benefit arrangements maintained in some beneficial societies or "lodges," and also by the use made of prepayments in so-called "contract practice." This last was an old scheme by which a family would pay a doctor in advance in return for service throughout the year, and it was sometimes advocated as paying for health rather than for sickness. How common the practice was is difficult to say.

American indifference toward health insurance may be plausibly explained by three other basic circumstances. The first of these has already been noted; that

is, the lack of confidence in ordinary medical practice. No one worried greatly about hospital costs, at a time when even the acutely ill were only too glad to stay out of hospitals. And in the large cities, the very poor could gain access to these institutions without charge. Meanwhile, the majority of patients were cared for in their homes by a single physician, so that their total medical expenses were relatively low. Thus the demand for medical service was moderate, and so likewise were the costs involved in such attention as was received. Neither of these circumstances indicated any need for a public system of medical care.

A third factor in the situation was the diversion of reform enthusiasms into a public health program. Both physicians and laymen were involved in this, and it is not easy to say whether the starting point lay in Medicine or within Society. Increasingly, after 1800, professional opinion came to emphasize the classical "airs and waters" theory of epidemics, and to give less heed to the dangers of contagion. There is probably no single explanation for this shift of opinion. Certain epidemics long viewed as contagious—notably of plague and of small-pox—were declining or had disappeared, and this may have decreased fear of contagion in general. But the epidemiologic evidence about others remained confusing, as can be observed in the endless debates about yellow fever, 1790 to 1900.

The growth of great cities probably had its influence, for the association of slums with a high disease rate could hardly be ignored. French physicians, after 1820, and English after 1840, employed statistics to prove that urban surroundings influenced morbidity and mortality rates, and the obvious conclusion was that an improvement in the environment would result in a decline of sickness. Hence the old doctrine of empirical sanitary controls received a new impetus. It seemed better to protect the poor through public preventive measures than it was to let them become ill and then to provide individual medical attention of uncertain value.

This program unfolded at a time when technology was becoming better equipped to deal with sanitary problems. Hence engineers as well as statisticians promptly stepped into the picture, and most of them were laymen. But public-spirited physicians were also in the van of the movement—Villermé in France, Southwood Smith in England, Virchow in Prussia, and Jewell in the United States. The latter organized the national sanitary conventions of the 1850's; and after these were broken off by the Civil War, like-minded colleagues formed a new American Public Health Association in the 1870's which has flourished ever since.

There is some evidence that sanitary reform actually did lower mortality in certain American cities between 1825 and 1875, and that it alone could have done more if it had received greater support (16). But the public, as usual, was indifferent except in times of crisis. State legislatures ridiculed the collection of necessary statistics and starved the pioneer state health boards of the 1870's. In that same decade Congress set up a National Board of Health; but when that able body spent so much as \$10,000 over several years, it was abolished because of its extravagance!

By the time that cities were willing to pay for real sanitary controls, chiefly

after 1890, bacteriology was able to provide more discriminating guidance to all public health measures; hence the potentialities of empirical sanitation were never fully demonstrated. But it is a mistake to laugh off this early program, as some later public health men have done, as a mere "matter of pipes and smells."

* * *

The public relations of Medicine have obviously been transformed over the last half century. The initiative seems to have been largely internal to Medicine during this recent era, although Society has by no means played a passive role. In the first place, medical bacteriology and related fields revealed much about the etiology and transmission of infectious disease, and so provided at last some rational guidance for preventive medicine. There ensued a discriminating application of sanitary controls, as well as a considerable use of active immunizations. The latter were employed both in individual practice and on a mass scale. The public health program was expanded accordingly, and the resulting decline in most of the major infections was truly impressive.

The new sciences also promised much for therapeutics, as in serum- and chemotherapy. Pharmacology, based on a correlation of advances in chemistry and in physiology, became more effective. Although early optimism about chemotherapy proved premature, and there ensued after 1920 what has been termed the "doldrum period," the sudden emergence of the sulpha drugs and the antibiotics after 1938 more than overcame temporary disillusionment (17).

Surgery, in the meantime, checked an almost reckless zeal which had been encouraged by the apparent safety of aseptic procedures. Surgeons became more careful and developed improved techniques. In the work of such men as Halsted, this field was correlated with physiologic research so that it finally transcended the tradition of an empirical skill. Daring surgery, because of its dramatic qualities, was especially apt to impress the public.

Other sciences played a part in these developments. One need only allude in passing to advances in biochemistry and biophysics, or to the striking new devices or instruments made available by physics and technology. Under the terms here used, these were all contributions by Society to Medicine. So important were they that some observers came to view medical science simply as a biologic field in which the physical sciences were applied. But again one must recall the inner core of medical tradition in pathology and the clinical areas, in terms of which the physical sciences may or may not be effectively employed.

Somewhat unexpected was the manner in which the structural pathology of 1850 led by the end of the century into a revival of humoralism in terms of endocrinology. The latter field, as well as the nutritional studies inaugurated at about the same time, was based upon research in physiology and biochemistry; and neither of these areas could be entirely fitted into concepts of localization and specificity. In consequence, medical thought began to be directed again toward the condition of the body-as-a-whole.

Parallel developments in psychiatry, in which there was a return to a psychology as distinct from a purely somatic outlook, supplemented the concept of

the body-as-a-whole with that of the total personality. This latter idea led, logically enough, into a rediscovery of personality factors in illness, which in turn opened up the significance of social backgrounds. At this point psychiatrists, converging on these matters from a medical standpoint, encountered social scientists who approached them in terms of the surrounding "culture." Such scientists will doubtless prove helpful to Medicine not only in relation to psychosomatic problems, but also in analyzing the human factors in professional relations which physicians have often taken for granted or dealt with in a rather amateurish fashion (18).

We need hardly be reminded that Americans took an increasing part in all these scientific advances. Dissatisfaction with the passive role of American science increased during the 1870's and was especially aroused by those returning here after receiving German training. Several medical schools took the first steps toward introducing research between 1875 and 1895, after which the example of the new Hopkins school encouraged a general reorganization of medical education in the better institutions. This reorganization was made nation-wide after 1912 by the impact of the Flexner report. Not only did the major schools become research centers, but nearly all the surviving schools began to turn out well-trained young doctors.

This whole revolution was an expensive one, since scientific schools were not profitable or even self-supporting as had been the commercialized medical colleges. But Society was able to meet greater costs because of the rapid growth of American wealth after 1890 and was willing to do so because public attitudes toward Medicine were profoundly altered during this era.

When the medical sciences reached a point at which they were clearly useful to mankind, even the most practical of nations was impressed. Indeed, the more pragmatic the outlook, the more was there a desire to assist medicine promptly. Respect for medical science was supplemented by regard for the better-trained physicians of the new dispensation. There were many expressions of these attitudes. Legislatures tightened up on licensing controls; while philanthropists made Medicine—hitherto completely neglected—their chief beneficiary. Instead of getting mediocre material, the medical schools began to attract the ablest college graduates—a most significant shift. Popular attitudes became enthusiastic, as expressed in the common use of the term "wonder" or "wonders" as applied to drugs, surgery, and "modern medicine." Even the movies indicated their regard in such films as those devoted to "Men in White," "Women in White," and "The White Parade." For a while, anything "in white" was good for boxoffice returns. And most public opinion analyses of the last two decades placed Medicine at the top of the professions (19a, b).

Confidence in Medicine and in medical men led, after 1900, to growing demands for medical services. The most obvious measure of this was the increasing resort to hospitals and the consequent expansion of these institutions out of proportion to population growth. At this point, however, things took a new turn. The very advances which made medical service more desirable also rendered it more expensive. Hence the more the masses sought professional attention, the

less they could afford it. Here was a paradox in the social history of Medicine. In the very act of overcoming popular indifference through scientific achievements, medical men inadvertently created a new difficulty in their public relations—the costs of medical care.

This issue first came to the surface of public discussion about 1912. Long before that, Germany had implemented compulsory health insurance in legislation of the 1880's; and in 1911 the Lloyd George ministry in Britain had started moving in the same direction. Within the United States, interest was growing in various social security programs, and this spilled over, so to speak, into the area of medical care. Could not the costs of illness be better borne if spread over the years by insurance? Such a plan appeared more feasible because of the advent, about this time, of commercial experiments with group insurance. Some limited but enthusiastic efforts were made to secure state laws providing compulsory health insurance, but the movement collapsed with the coming of World War in 1917 (20). It reappeared only with the advent of depression in 1929, after which economic tensions gave the issue a greater urgency.

Subsequent debates over health insurance are too well known to bear repeating here. So, too, are the parts played therein by welfare organizations, medical societies, government agencies, Congress, and the national administration. By no means a minor aspect of the story has been the rapid expansion of voluntary health insurance, which is viewed by many as preferable to a government program. The point to be emphasized is that, once again, Society and Medicine are interacting, and this time with a vengeance. The outcome is not yet clear, but we are certainly living through an era of transition in the relations between Society and the medical profession. This transition involves not only new plans for meeting medical costs, but also new arrangements for providing medical service—notably that of group practice. It is hardly necessary to elaborate on this latter theme at The Mount Sinai Hospital.

* * *

Implicit in all arguments for compulsory insurance was the assumption that Medicine had done, or at least could do, great things for Society. "Organized medicine" did not always appreciate this compliment under the circumstances, but there is no doubt that it was genuine. Before concluding the discussion, it were therefore well to raise the question: how well founded was this public confidence in medical achievement? An answer to this should suggest what Medicine has indeed accomplished in our time; as well as what, perchance, it has left undone. Having glanced at the continuing influence exerted by Society upon Medicine, let us now focus finally on the reverse impact of Medicine upon Society.

Public confidence was certainly founded, in some measure, on actual achievements. Everyone is familiar with the spectacular declines which occurred, after 1900, in gross mortality rates as well as in those for particular diseases. Perhaps more significant was the increase in life expectancy, especially at birth but also at other ages up to about fifty. Careful estimates have indicated that expectancy at birth in Massachusetts, in 1790, was only about thirty-four years; by 1900

this had risen to forty-six, and by 1930 to about sixty (21). Since then it has gone even higher, especially for females—a fact which I cannot record, in passing, without a slight sense of masculine grievance.

Social factors doubtless accounted in part for the increase in life expectancy after 1900, as well as before. It is also possible that changes in the virulency of infecting agents or other obscure biologic factors played a role in the natural history of certain diseases. Yet the case for a direct medical influence is much stronger in this recent period. One hardly need labor this point, but reference may be made to such analyses as that done by Winslow for New Haven. He found that the decline in five diseases—attributable in each case primarily to medical means—accounted for ninety percent of the drop in crude mortality between 1887 and 1926 (22). Most of the result could be ascribed to prevention rather than cure, but the preventive program had been a medical rather than a merely empirical one.

The declining death rate and rising life expectancy after 1900 speeded up population changes already under way during the preceding century. Despite the concomitant drop in the birth rate, the population increased; and at the same time its composition was altered by an increasing percentage of those in their later years. There ensued a revival of Malthusian warnings, a renewed debate over birth control, and various efforts to adjust the relations of the older age groups to the rest of Society. All of these outcomes can be seen in even bolder perspective in so-called backward nations, where population increases which follow upon the introduction of preventive medicine are unchecked by declines in birth rates. In so far as Medicine has been responsible for these developments, it has plainly become one of the major forces at work in modern Society.

Meanwhile, Medicine had to cope with certain repercussions from success within its own province. The survival of a growing proportion of the population into old age automatically advanced the incidence of diseases typical of that level. Hence, as the morbidity from infectious diseases declined, that from chronic and degenerative disorders mounted in startling fashion. One could argue that this was to be expected and was indeed a sign of "progress," for a postponement of death had long been viewed as an ultimate purpose of Medicine. In modern society, at least, the death of children or of young people is considered inherently more tragic than is that of their elders. A few thoughtful physicians did question this, however, on the ground that death from an acute infection was more merciful than that from a lingering illness in the modern manner (23). Such considerations pertained to individual experience.

The matter may also be considered from a social viewpoint, where again one argument can be pitted against another. Death from acute infections, in the past, carried off large numbers of children and young people. They succumbed at the threshold of their lives, before they had made any contributions to Society. No nation can well afford such a loss of its most energetic or promising elements. Over against this, however, must be balanced the burden which Society now carries in the form of the chronic illness—indeed of the very exist-

ence—of great numbers of elderly people. We are now in the midst of difficult social adjustments to this latter situation, in terms of social security, hospital construction, and rehabilitation programs.

Is this burden made greater by an increase in chronic illness out of proportion to population changes? It is ominous if certain major diseases are increasing, as it were, in and of themselves. The evidence is not too clear. It has been claimed, for example, that such a trend is under way in the case of cancer; but, on the other hand, this is denied in the case of cardiovascular diseases. But let us assume the worst—that there is an inherent increase in certain chronic diseases. If so, there are at least three conceivable explanations: (1) that the trend is due to obscure biologic changes; (2) that it is a product of Society, that is, of current manners and customs; and (3) that it can be ascribed to Medicine itself.

The biologic interpretation seems the least plausible, in view of the recent and rapid character of apparent increases in such morbidity and mortality. Speculation on Society's responsibility for chronic illness is familiar enough, and is implied in the oft-expressed desire of modern man to "get away from it all!" The brunt of the blame usually falls on industrialization, working conditions, and the mode of life in urban communities, although our rural areas are hardly so exempt from morbidity as to justify much of a claim for "the simple life." In any case, a desire to return to this is plainly unrealistic. As a matter of fact, anthropologic studies have revealed a considerable amount of chronic illness, including mental, in even the most primitive societies. This is not to say that the tensions peculiar to current living bear no relation to illness; indeed, studies in the psychosomatic realm plainly indicate that they do. But we are hardly yet in a position to assay the degree of responsibility which is involved in relation to the total problem.

As far as Medicine is concerned, one may admit that the general optimism so common among physicians as well as laymen in the past half-century requires qualification at certain points. Even the "wonder drugs" have their limitations and the "conquest of infectious diseases" is by no means complete. But the important question is not whether Medicine has left certain things undone, since that is to be expected. It has never claimed to be infallible. The major question is whether Medicine has, inadvertently, contributed to present difficulties by doing those things which it ought not to have done?

Let us assume as justifiable those increases in degenerative and chronic diseases which result simply from survival into the later years. Are there, however, additional increases which can be ascribed to medical science and practice as such? It has been estimated that some 25,000,000 Americans are victims of chronic illness, and that perhaps half of these are under forty-five years of age. Of this latter half, a century ago, a large part would have died before this from infectious diseases. Modern practice has kept them alive, either by prevention or cure, and claims credit for the result. But if the result is only chronic illness—even prior to old age—what then?

The discussion brings one back to the basic concept of the nature of disease. Two centuries ago, when this was viewed as a general state of body and mind,

many of those who perished early were written off as the victims of "weak constitutions." Even during the last century, under the influence of Malthusianism and later of Darwinism, some opposed public health programs lest these permit the survival of "the unfit"; that is, of those who had such weak constitutions. If now we revive the concept of a generalized disease condition—as Medicine is doing in some measure—it appears that this condition in the individual may both precede and follow the attacks of specific diseases. It has been said, in this connection, that the individual is not sick because he has a particular disease, but rather that he has the disease because he is already sick. And this being the case, the "cure" of the specific disease still leaves him—after much expense—in his unregenerate state of original illness.

The evidence for this lies, of course, in the degree to which many who are "cured" of this or that survive without positive good health, or soon become victims of what are apparently other disorders. In this sense, Medicine apparently is contributing to the survival of the unfit, with all the burdens to individuals and to Society which this entails. The only way out, it has been suggested, is for Medicine to abandon its still-persisting emphasis upon specificity, and to return to the tradition of treating "the whole man" in relation to his total environment. To quote Galdston (24): "Without a new and most competent orientation as to the nature of health and disease, medicine is doomed to sink deeper and ever deeper in the quagmire of its curative efforts, never catching up with the load of illness which burdens the sick, society, and the profession."

This is a pertinent analysis which, presumably, will receive more serious consideration as time passes. Certainly the limitations inherent in nineteenth century concepts of structural pathology and specificity are becoming ever more apparent. This, of course, is not to say that they were useless in their time or that they have ceased to be of any utility today. Like all scientific concepts, these must be maintained, modified, or abandoned on the basis of available evidence. Some persons seem to acquire a disease because they are sick, but others are apparently sick because they acquire a disease. It is not clear that all who "catch" a given infection, if exposed to the causal agent, are those already "sick," at least not in any ordinary sense of the latter word. Nor is it clear that all those who are cured of this disease by antibiotics remain thereafter in ill health of one sort or another. A qualified employment of the concept of specificity is therefore likely to remain useful in therapy as well as in preventive medicine.

Some caution may well be exercised, moreover, in interpreting the burdens now placed on Society by curative Medicine. That the burden is there is unquestioned. But how far it is a greater burden than was carried by Society in the past—or than would be carried today had it not been for a specifically-minded Medicine—is hard to determine. It is not to be forgotten that there was a vast amount of chronic illness in the youthful American population of the last century, although few statistics are available for measuring this. Perhaps these people were spared such an incidence of heart and vascular conditions, or

of cancer and of diabetes as now obtains in even that part of the population which is under sixty. On the other hand, malnutrition, malaria, hookworm infection, and tuberculosis were far more widespread than at present, and insiduously undermined health at all age levels.

Granting all that is said about chronic illness today, the historian often gets the impression that American communities of a century ago were actually more "sickly" than are present generations. If so, whatever increase of chronic illness may have resulted from recent curative practice, has been more than counter-balanced by the decrease in such illness resulting from other measures.* This in no way implies that present efforts to deal with "the whole man" are undesirable, since these offer some hope—just how much is not yet clear—of preventing or ameliorating even present types of chronic illness.

To sum up, the historical perspective suggests that the influence exerted by Medicine in American Society over the last century has certainly been fortunate in some respects, possibly unfortunate in others. The story hardly justifies the unbounded optimism of the past generation; but neither does it lend itself to such pessimism as other aspects of our history sometimes inspire. My own conclusion is that the nineteenth-century idea of progress, though sadly shattered now, still retains elements of validity; and that no better case for this can be made than by recalling the historic interplay between Medicine and Society

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* This point illustrates the value of an historical perspective in relation to current evaluations or sociologic analyses—a value which is fully appreciated by authorities on the sociology of science in general. See, e.g., Barber, Bernard and Merton, Robert K.: *Brief Bibliography for the Sociology of Science*. *Proc. Am. Acad. Arts and Sciences*, 80: 140, 1952.

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MEDICINE AND SOCIETY: THE BIOLOGICAL FOUNDATIONS

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We are assembled to celebrate the achievements of 100 years of service and progress. We pause to commemorate names that have graced the period and the nameless thousands who have contributed their labors to make it a success. Yet we pause but briefly. Tomorrow we shall press forward again, toward a new and even brighter future. To keep perspective, shall we say, we merely celebrate passing the half-way mark toward the bicentenary of this illustrious institution, and many more happy returns thereafter? In such long-range perspective, we look back upon the past not just to glory in its achievements, but to get the bearings by which to chart our future course; not just to gloat over how well we have done, but to get pointers on how to do even better. I thus hope you will bear with me if I discharge my assignment on "The Biological Foundations of Medicine," in a spirit of constructive evaluation, rather than mere anecdotic reportage.

That medicine must rest on a firm foundation of biology, is a truism. Biology is the science of life. Man is alive in a world full of other life relevant to his existence. In his basic constitution, functions and reactions, the human organism is a biological system, developing, growing, maintaining itself, responding, behaving and adjusting according to the laws governing all life. Thus, to dwell on the dependence of medical progress upon biological knowledge would seem as redundant as to labor the fact that engineering is rooted in physics, chemistry and mathematics. In fact, throughout history, medical motivation and observation have added to biological knowledge as materially as has biological understanding to the advancement of medicine.

However, let me make clear at the outset that I realize that this does not imply that medicine is just "a branch of the biological sciences," as it is sometimes called in pardonable short-hand language. Medicine is rather a hybrid of two parental lines, only one of which lies in the sciences of objective measurement and logical deduction, while the other stems from the subtle but subjective powers of evaluation and judgment of the human mind, to be tapped whenever the doctor faces the individual patient, the single case in its uniqueness. Science does not deal with unique events. It only encompasses them. It deals with the general rules, usually statistical, in common to large numbers of cases,—the average behavior. Physics does not deal with a particular electron or a given atom; meteorology not with a specific cloud in its uniqueness. No two cells will ever behave exactly alike, no two disease courses duplicate each other down to the last detail. Lest this semblance of indeterminacy disquiet you with the suggestion of indeterminism in the universe, let me point out that it need mean no more than our own inability to predict precisely and infallibly the individual event. The physicist, knowing full well the laws of wave motion, which all waves

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must obey, is yet unable to predict the precise shape of any particular wave on the ocean, moulded by a unique constellation of currents, winds, wakes, tides, reflections off the bottom and backwash from the shores. Predictive science takes an interest in individual cases only for what they may hold in supporting old, or directing new, generalizations and theories. It then discards them as non-recurring items. Scientific prediction can be positive about what cannot happen and what might happen, but it can only approximate reality in anticipating just precisely what will happen in the individual event. This is where the physician cannot afford to be a scientist. His interest must sharpen as it focusses on the single, unique and non-recurring specimen, the human patient whom he wants to help.

There are thus two strains running through medicine, one of impersonal scientific method, which furnishes the rules and tools for guiding judgment, and one of personal decision applying guided judgment to the unique case at hand. The trend over this past century has been for the scientific strain to grow in vigor and volume. This should be no cause for alarm, since the two strains are not competitive, but supplementary. And truly in the expanding universe of human welfare, there must be plenty of room for both happily to expand in unison.

As science with its method and knowledge and tests and checks provides personal judgment with ever safer guides and narrower margins for error, it expands legitimately into what the ancient ministers of the healing art might have claimed to be their proprietary rights. Commensurately, however, it frees time and energy for the cultivation of human values and the powers of human application. Let us not overlook that the human body contains some of the subtlest precision devices of discrimination and evaluation. Our eye can detect a few quanta of light, our nose a few aromatic molecules. True, we can design technical apparatus of equal sensitivity to register elementary stimuli, but for the perception and evaluation of the most varied patterns and combinations in which they appear in nature, there is no substitute to that discerning power of the human mind which we call judgment. The time and effort that science saves us on the one hand could then be profitably spent on training and sharpening by practice those peculiarly human faculties.

There is a danger, though, that we may fail to develop them to their full power or let them atrophy from sheer disuse. Then, of course, as you give withered muscles the support of braces, so the sciences will have to come to the rescue of withered minds with the poor substitute of automatic rules, preventing at least the worst malfeasance and the fatal error.

Perhaps we are heading that way. When there are not enough teachers of native talent to go around to fill the needs of an expanding educational system, particularly when the really good ones cannot be attracted to a station of economic and often social inferiority, society, depending now more on the lesser lights, has to protect itself against incompetence by giving them some hard-and-fast mechanical rules of conduct. Likewise, if an expanding program of medical care should fail to fill its quota from those with native talent and calling for the

profession, science will have to provide ever firmer guide ropes to make sure that even those with blurred vision will not fall off the safe trail, dragging their charges with them. Science will never dehumanize medicine. But conceivably it might one day be called to the rescue of a dehumanized medicine.

I made these introductory remarks to convince you that I am not one who would grant a monopoly to the scientific approach to medicine. Having made this clear, let me then proceed to deal with those aspects of medicine which lie definitely within the right of domain of science. If medicine is to rest on a firm base of biology, let us examine that base to see whether it is being adequately broadened, strengthened and secured to support the continued growth of medicine.

Biology is in a state of flux. The most dramatic change that is occurring in our days, the key to the understanding of all the rest, is what might be called our industrial revolution, that is, the rapid conversion of our science from small-scale workshops of individual craftsmen and apprentices to the mass proportions of an industry, with all that goes with it: more workers, more administration; higher production quotas and more specialties; more rote and less call for initiative; standardization mixed with the rule of fashions;—yes, even vested interests and jurisdictional disputes. Research, education, publication, budgetary policies,—they all reflect this tide as they grope to adjust to the new pattern.

In the conviction that the change is here to stay, undoubtedly for better rather than for worse; that it calls for major adjustments; and that such adjustments can be made rationally and methodically only if we see clearly where we are heading; I shall try to outline some of its principal symptoms. They are:

- 1) an organizational regrouping within biology;
- 2) progressive fragmentation of biology into innumerable specialties, with corresponding loss of unity and communion; countered by
- 3) deliberate efforts at reintegration and cross fertilization by combination of formerly separated lines; particularly new tributaries from the physical sciences, and the advent of team work;
- 4) spectacular progress in certain favorite channels of massive application, at the expense of relative starvation of other urgent tasks; hence distortion of proportions of the field as a whole;
- 5) a dearth of pioneering spirit because of reduced motivation and opportunity for adventure, along with heightened concern for personal and intellectual security; perhaps also some decline of standards of scholarship and workmanship, trading quantity for quality, and
- 6) above all, a growing realization of the impact of science on human welfare, and the growth of a mature sense of responsibility, of the scientist toward society, and, in traces, of society toward the support of science.

The arguments for these six points are now to follow.

First, as for the grouping and classification of the biological sciences, it may be useful to remember the artificiality of the labels under which they run. As Abraham Flexner said in this connection, "Medicine is an indefinite portion of the vast field of biology. . . . For purposes of effective attack, the area to be

explored, itself only tentatively marked off, has been provisionally divided, but the several portions really have no distinct individuality. On the contrary, they merge into one another and are liable to regrouping whenever they are surveyed from a new point of view." While our teaching and research system still employs the classical pigeonholes of zoölogy, botany, bacteriology, anatomy, biochemistry, physiology, pathology, and so forth, the study of life actually forms a continuous spectrum from which different interest groups have merely cut out different absorption bands depending on their own absorptive faculties. Such subdivisions are not only an administrative expediency but can be highly effective when they have task-force character, that is, are charged each one with occupying a well-defined sector of a field. But just in the latter sense, those traditional designations have lost much of their original meaning. A colleague* recently defined a zoölogist quite pertinently as a man who does his work in a zoölogy department; were he to do the same work in an anatomy department, he would be classed as an anatomist, and in a physiology department, as a physiologist. A glance at modern cell biology, endocrinology, or neurology bears out this operational definition. The old lines of demarcation have become erased and the fields they used to circumscribe have become, as Flexner put it, "liable to regrouping." This regrouping is definitely under way.

Many of our traditional classifications were based either on forms of life, as in bacteriology, botany and zoölogy, or on methods of approach, as anatomy (for dissection) and biometrics (for measurement). With the growing realization of the general validity of certain basic principles common to all forms of life, a more natural organization of biology according to inherent principles is gradually superseding the old pattern. Thus investigators and teachers have begun to draw promiscuously on bacteria, plants, animals and man for knowledge and illustration of the principles of cell structure, metabolism, growth, heredity, excitation and coordination, adaptation, ecology and evolution. Many of the greatest advances of biology have come in places where different specialties have combined forces in conjoint study. The spectacular development of genetics in this country has profited immensely from the correlation of facts from such diverse fields as cytology, animal and plant breeding, biochemistry, immunology, statistics and taxonomy. As a result, the old alignment gives way to a new, more natural and more consistent order. The important thing in the present context is that in this new order, the biology of man is due to be included as an integral part. Genetics courses will encompass human heredity, development be taught with reference to wound healing and tumors, and animal behavior, with an eye to social psychology. But even as old disciplines escape the straight jacket of obsolete trade marks and become confluent, the new currents again break up into new local whirlpools, and fragmentation into ever more compartments goes on at an ominous pace; which brings me to my second point,—the splintering process.

Fragmentation goes with specialization, and specialization is a mark of scientific progress. Mastery requires concentration, which means narrowing. The gibe about the man who gets to know more and more about less and less is

* Alfred S. Romer.

not quite just. Science needs that man. The only question is whether it can entrust its progress wholly to his hands? Our answer to this question today may shape or warp the future course of biology and medicine.

Subdivision of tasks under a common plan and with a common goal in view is good accepted practice. A common goal and common rules will hold the parts together. Splintering into isolated and independent columns, therefore, is something that only a science of sufficiently advanced maturity, which has a common goal and common rules, can well afford, a science whose basic framework of concepts, principles, terms and units has become consolidated and unified. Physics has evidently reached this stage, and chemistry is near it, but biology most definitely is not. Biology is only just emerging as an exact science. It is still groping for its basic principles and concepts. The blank spots on its map of fundamentals are legion. Its vocabulary is still fraught with the subjective terms of primitive and non-analytical observation, its problems are formulated in ambiguous symbols. There is no common master blueprint from which the various specialists could each take home a different assignment for independent piece work, with reasonable certainty that their final products, when assembled, would fit together into a rounded and harmonious whole.

The point I wish to make is that biology can continue to make healthy progress only if its task forces start with a comprehensive view of the problems in the field, keep this total perspective in view and do not lose it when they retreat into their various working quarters. This requires not only effort but determination. The difficulty grows as the horizon widens and information grows in bulk. Helpful devices are interdisciplinary conferences, review articles and informal exchange of views. Biological education likewise is beginning to present an integrated picture of the province of biology, rather than a smattering of miscellaneous data. However, all these countermeasures are still so thinly spread that unless greatly amplified, they could hardly offset the growing momentum of disintegrative over-specialization.

Let us take, for example, the nervous system. It represents problems of molecular organization, histological structure, geometry of connections, biochemistry of metabolism, chemical and electrical correlates of conduction and transmission, pharmacological response to drugs; problems of coordination, specificity, integrative, regulatory and interpretative functions and their derangement, as well as the whole problem of the developmental mechanisms through which all of this has come about. So the histologist, physiologist, biochemist, embryologist, psychologist, psychiatrist, and so forth, pick out each a partial aspect, analyze it with the best of techniques available, according to the most rigorous scientific standards known to them, only to discover, if and when they come together to compare their conclusions, that these do not quite jibe. They come up with as many different versions of the brain as there are aspects, overlapping in good measure, to be sure, but largely also inconsistent and conflicting; and yet, the brain is still one and the same. I could cite several recent symposia in ample illustration of this contention. Yet I have chosen this example because the study of the nervous system is perhaps one of the most heartening

examples of active resistance to specialist isolationism. Here, clinician and anatomist, psychologist and physiologist, cytologist and biochemist, and other cross-combinations, join forces to clarify their common objects and perhaps straighten out their inconsistencies. And so in other areas, such as genetics. But there are fewer and fewer people who are still sufficiently conversant from firsthand experience with the basic facts and problems of the whole of biology to arrange their own research and teaching in the light of such over-all perspective. Most others now inherit a narrow specialized sector of the field and learn about the rest only in formalized and watered-down second-hand tales—or fables.

This whole development is, of course, a corollary of the growth of our science. In the old days, which means not much more than a quarter of a century ago, a biologist still had training and experience in all the major manifestations of living systems, and it was still within the grasp of a single man to give a fairly comprehensive and well-balanced lecture course in biology in its totality. A single journal such as the *Journal of Experimental Zoology* would carry articles on development, genetics, protozoology, nutrition, insect physiology, endocrinology, ecology, animal behavior and what not. In those days, it was easy to keep one's bearings and balance in the total scheme even as he applied himself to rather specialized investigations. But nowadays, we tend to bring our students up to stay in rather closely demarcated channels. Scientific journals and societies frown on diversity and purify their contents so as to embrace smaller and smaller parcels of subject matter or technique. And making virtue of a necessary evil, they are begetting a narrow-minded sectarianism, which biology in its state of immaturity and loose coherence can ill afford.

Communing between different branches of biology, one often finds that they have highly unrealistic, if not fantastic, notions of each other's subject matters. What is disturbing, is not that they disagree, but that they do not sense it or, worse still, do not care. I am not speaking of conflicts that cannot be resolved but of the conflicts, as well as opportunities, that just go unnoticed because of self-inflicted myopia.

I could give you endless examples from current literature. Of course, there have always been seclusive tendencies in our, as in any, science. But never before could the resulting incongruities assume the perilous mass proportions made possible in our day by the inflated volume of scientific production. The danger that the various segments of biology will succumb to the centrifugal pull and fly apart on separate tangents is a very real one.

This danger of particularization in biology is partly offset by the reverse tendency of divided branches to combine in the attack on certain focal problems. This brings me to the third point on my list. Desirable as this cooperative trend is, it sometimes also aggravates the problem. This happens in those cases in which supposedly converging lines have different notions of just what their common object is. For instance, there is a growing and welcome influx into biology of students from the physical sciences, who have had no first-hand acquaintance with real biological phenomena. In their innocence, they then often contrive

models of organic systems so utterly fictitious that any resemblance to living beings is, as they say in the movies, purely coincidental. Models must bear some pertinent relation to the real thing. To choose them right, one has to know the real thing. Otherwise, one ends up with something, perhaps quite interesting in itself, but wholly irrelevant to the elucidation of life. Even so, the principle of conjoint and concerted effort has been one of the potent antidotes to our growing schisms.

The expansion of the interests of the biologist into the clinical sphere, as well as the growing preoccupation of the clinician with fundamental biological facts, introduces a similar problem. I was brought face to face with it during the war years, when I had the privilege of cooperating closely as a biologist in clinical problems of nerve repair. I found the laboratory man, including myself, and the clinician, with notable exceptions, about equally matched in their rather primitive notions of the other's domain, but I also soon learned how quickly one can gain common perspective provided he really wants to. Unfortunately, as I shall explain later, lack of perspective does not automatically engender the will and desire to acquire it.

Fragmentation without commensurate restoration of total perspective leads to a trend I list as number four. Let us call it the draining force of favorite and fashionable lines. The principle is old. A pioneer trail, frequented heavily, develops into a boulevard. Such traffic arteries have a way of draining competing smaller roads and obliterating them. Well, in biology, too, the paths laid out by pioneers, improved and widened by their followers, tend to become popular and crowded highways attracting those who look for easy travel. People flock into them because of some prophecy or illusion that at the end lies the key solution to this or that fundamental problem. Yet, many such supposed royal roads have turned out to be roads to nowhere, and in our present state of groping uncertainty, unable to predict just where the breaks will come, we cannot possibly afford to gamble on a few single-tracked advances in force if this involves, as it does, the risk of draining vital resources from all other, and perhaps potentially more pregnant, sectors in between.

This is an irrigation problem. The heavier and swifter the major streams, the larger and more potent will be their drainage area, so that instead of a uniformly irrigated and cultivated land of knowledge, we will end up with an erosion landscape with a few major fertile canyons, but arid mesas, high and dry, between them. A gold rush justifies itself by its returns. But when its claims rest on no firmer base than rumor, misinformation or promoters' optimism, it does incalculable harm, not by its own futility, but by diverting prospectors from broader explorations. I am afraid, our social hydrodynamics is working in just that direction.

In biology, this trend is relatively new. In the old days, and not so long ago at that, workers engaged in biological research were relatively few in number, with a high proportion of independent pioneers, and funds were scarce. No single pet line could thus undergo undue aggrandisement. Now things have changed. As manpower, funds, facilities keep growing, they are increasingly

funnelled into established lines to the point of inflation, instead of being more equitably apportioned over the entire research front for ever new probings into the unknown. I use the military term "front" advisedly. For what else is science but a campaign to conquer the territory of the unknown by all the rules of strategy and tactics, advancing in a closed front probing for weak spots, hoping for breakthroughs. Now, it is sound strategy to widen a breach; but it is bad strategy to deplete a whole front in favor of a breach that has not yet become a breakthrough. Many current lines in biology have actually been singled out for preferential support only because of the honest, if ill-founded, trust that they indeed are breakthroughs. The dignity of official recognition often helps to reinforce that trust. Yet, it cannot be stated too emphatically that there is at present not a single area in which sober and objective evaluation could justify such trust. What happens then is that the far-advanced and isolated columns eventually get stalled and have to wait, after all, till the rest of the front line, far behind and sagging, has been pulled up abreast.

Let me give you a few examples. Our progress in the identification, isolation, purification and even synthesis of hormones has been truly impressive. But contrast the enormous volume of this work with the wholly inadequate attention and effort spent on discovering how a hormonal target organ can respond selectively to its proper hormone. Or compare the remarkable advances in our knowledge of enzymatic, metabolic and electrical properties of single neurons with our virtually complete ignorance of what makes them operate in harmonious coordination in the system; or the considerable volume of work on mitotic poisons with the dearth of interest in what causes mitosis in the first place; or the extensive studies on the metabolism of maintenance, with the almost complete neglect of the metabolism of specific differentiation and growth. Such imbalance is unsound and arbitrary. If only a small fraction of the traffic were rerouted from those favorite lines into their neglected counterparts, biological research would be restored to healthier proportions. But to achieve this, requires the recovery of free and broad vision, now curtailed by the high walls of the grooved currents.

Thus fragmentation not only threatens to destroy perspective but facilitates the distortion of research and teaching into bizarre patterns. As our science advances, we see more and more new problems opening up, more of the old conclusions in need of rescrutiny, but we have neither the manpower nor the resources needed to man this widening front, for they are being sucked into the easy channels of mass application, and just where the need for exploration is greatest, explorers are the scarcest. Adding to this the fact that as the number of scientists increases, the gain tends to accrue more to the ranks of the less imaginative than of the highly gifted, our predicament is clear: it is not that we shall learn more and more about less and less, but mostly the converse, that we shall remain so sorely ignorant about ever more and more.

Let me just point out that with all our wonderful progress in biological research and theory, most of our core problems still lie in deep obscurity. We do not know the physical basis of intracellular organization, the principles that

sort biochemical processes and diverse molecular realms in space without the aid of rigid mechanical frameworks. We do not know the first thing about what causes orderly substance transport within cells, nor do we know the motive mechanism of cell locomotion. We do not know how cells recognize each other, their foods, their enemies, and how they can react selectively to their environment. We still have no more than shrewd guesses about the mechanism of protoplasmic reproduction that we call growth, the process in which constituent chemical units fall into places all at once to replicate a model compound, and only in the presence of the latter; nor do we know what activates and checks and reawakens the powers for such growth in development, disease and aging. Even less do we appreciate, let alone understand, the supracellular principles of field character which order the cellular community both in development and in the coordination of our nervous functions, and whose disturbances may yield freaks in the former case, mental disorders in the latter. This is just a small but fair sample of our state of ignorance.

How is it possible that in this state of ignorance we commit ourselves with such abandon to the pursuit of relatively few and far-between courses, at the risk of the collapse of the whole front? True, fragmentation has set the trend, and loss of perspective has blinded us to its risks. But the basic motivation to follow it lies, I believe, elsewhere—in the psychology and sociology of contemporary science, and this brings me to the fifth, and perhaps most important item of my thesis: the personality of the investigator.

You realize, of course, that the well-channeled roads of mass traffic are also the ways of least effort and resistance, offering the security that lies in numbers, and the comfort that comes with conformance. To travel them does not call for the vision and daring and fanatical devotion of the pioneer. Procedures are neatly mapped out, equipment ready made, and tangible results are the more certainly assured, the more narrowly circumscribed the task. While the contribution of the individual may be infinitesimal, the cumulative product of the crowd adds up to an impressive record in which each participant may claim credit. The risk is small and the reward assured. And this, of course, appeals to those who crave security. Coincidentally, our prevailing system of research support by project grants plays in their hands and confirms them in their attitude.

The project system, which allocates funds for a specific purpose, is admirably suited for developmental work, that is, for tasks that can be clearly circumscribed because we know essentially what we want to find and can spell out in detail how to get there. It likewise is suited to the testing of an existing theory, to the broadening of an existing set of data, to the improvement of an existing technique or to the elaboration of existing doctrine. At any rate, it places a premium on the continuation of existing trends rather than on the exploration of new ones, and the very source of scientific discovery, the inductive process, the prospecting of the wholly unknown, is given little of a chance.

Now, fortunately most of the agencies endowing research, whether public or private, have come to realize this situation and do not hold a grantee to the

delivery of the specific goods he has contracted for, as long as he keeps on delivering some useful goods. But although they subscribe to the philosophy of some free, unprescribed and unpredictable research, they feel ill at ease for fear that the powers whose funds they administer might disapprove. They fear that neither the public at large nor its representatives in government nor special interest groups, by and large, are ready to leave the disposition of research funds wholly to the discretion and conscience of the investigator with no specifications and deadlines for delivery and accounting. Nor would one want to advocate such policy for general adoption. But I suspect it is precisely this eyeing of possible public reaction that makes research money, except for periods of national emergency, flow more readily into conservative projects of predictable outcome than into more imaginative ventures of greater risk, yet infinitely more promising profit yield. Thus the average investigator and his average public sponsor are actually well in accord: they both want to play safe—security foremost.

The roots of this development do not lie wholly in sociological and economic conditions. Part of them lie simply in our education, and this realization points to a remedy. A generation that is raised, for better or worse, with security, rather than aspirations, and with comfort, rather than exertion, as the designs for living, is after all not well equipped to take the gamble of a pioneering life in science, or even to underwrite the risk of others willing to take it. If in addition industrial and government jobs in development work will keep on commanding higher salaries than do academic positions, the hope for broad advancement of the biological sciences might indeed look dim.

Fortunately, however, there is a brighter side to this. I do not believe that the course I have just described is inexorable and could not be reversed by a sound educational philosophy. Pioneering, after all, is not a mass procedure. It does not take many men to make a discovery, and we have a goodly quota of apt candidates in our student population. I see them daily: curious, determined, bright, and eager to advance the frontiers of science. Trustingly they turn to us for guidance, and what do we do? This may be a harsh pronouncement, but we misguide them. We misguide them by giving them a biased and over-optimistic picture of our present state of knowledge. While we dwell on our accomplishments, of which we may be rightfully proud, we are less candid about the vast expanse of the unknown yet to be conquered. We give them hard and fast answers where uncertainty ought to be stressed, we pass debatable opinions for facts, we pretend knowledge where there is none by hiding plain unknowns behind suggestive allusions. In short, we impart to them a sense of smug satisfaction that the essential information is all in and that nothing remains to be done but to round it out and fill in some missing links. How can we then expect them to see what we so carefully conceal? Instead of training them to face up to the unknown, we help them turn their backs to it. And why do we do this? Again, to give them a sense of security, I suppose; a false security, of course. This we can change.

Another thing we do is instill in these young minds a grossly overmagnified

picture of contemporary accomplishments, dwarfing appreciation of the vast stock of older data on which they rest. Again, if biology were in a state of maturity comparable to that of the physical sciences, that stock of knowledge would by now have become fully ordered and incorporated in a consistent code of rigorous and universally accepted principles and laws. However, as I said before, biology is not yet in this lucky age. True, a few areas, such as genetics or evolution, have managed to compress a large number of empirical facts into some valid generalizations. But most areas by far have not yet succeeded in finding conceptual formulae that would permit them to dispose of the record. Much less do we have a system of rules and principles that would tie the various areas into a conceptual unit. Then how can we justify the careless unconcern by which we let the record of the past recede into oblivion before it has been properly extracted and condensed into some master concepts?

Therefore: Let us restore the scholarly approach which takes a balanced view, derives the present from the past and goes on to project it into the future, with no undue enlargement of the present. This will give to the student saner historical perspective and a calm sense of continuity of progress and stability of course. As matters now stand, it is not rare to hear an eager student who is quite up on all current literature, refer to work done fifteen years ago as "way back in 1937." He registers surprise at the discovery that competent research was done even in those ancient days. Of course, he is surprised. Turning the spotlight on the present, we tend to hold the past in relative obscurity. Why don't we let our students partake in the host of fruitful ideas and challenging problems buried in the older literature? Is it perhaps again because of the sense of security that comes with confinement?

This is the point where we can turn the tide, but it will take courage. I firmly believe that we can lift biology from its deepening ruts back to the open plain of unobstructed vision and broad advance by reemphasizing leader spirit and attracting more leadership talent. To do this, we must humbly acknowledge the vastness of our ignorance, point to the exciting vistas of discoveries yet to be made and to the countless opportunities. By stressing the challenge of the unsolved biological problems and indicating ways to their solution, we can attract and inspire the superior minds who now see little scope for their ingenuity in a field part nature lore, part technical routine, with not much premium on daring enterprises. This is a real task for our educational policy, and granting concurrence of research, administrative and economic policies, it can succeed.

This optimistic note gives me my cue to turn from anamnesis and diagnosis to the prescription of a proper therapy.

From what I have said the case is about as follows. Biological science is surely coming into its own. Its volume grows, its impact on medicine, public health and agriculture becomes ever stronger, awareness of its social implications spreads. It truly aspires to becoming the science of the century. It is profiting from the advances of its more mature sister sciences, physics and chemistry, by adopting their techniques and methods of evaluation, as it is also building the scientific underpinning for the even younger social sciences of

psychology, sociology and anthropology. The mystery of life is yielding to the piercing intelligence of its most mysterious product, the human mind. Enlightenment replaces obscurity, and the will to understand prevails over obscurantism. Progress is truly grandiose.

But as I have tried to indicate, this rapid progress carries inherent dangers, of precocious over-specialization, loss of cohesion and perspective, and others. The symptoms are clear enough and point to the proper therapy. Treatment is indicated on two planes—that of administrative structure and that of the human individual. Neither alone can have effect without the other.

Let us turn to the former first. The splintering of biological sciences will, of course, continue unabated. But this loosening up also provides an opportunity to reweave the separating threads in new and fruitful combinations.

As a practical example of such regrouping, let me cite the reclassification of the biological sciences which I have recently devised for administrative use within the National Research Council, but which since it reflects our modern trends might be applied more widely. It sorts biology into six major areas based on inherent principles of life as follows:

- 1) *Molecular biology*; concerned with the elementary compounds, their interactions, transformations and the attendant energy balance;
- 2) *Cellular biology*; the behavior of the organized cell, especially the coordination of molecular events underlying orderly structure and function;
- 3) *Genetic biology*; covering the laws and mechanisms of heredity, that is, the continuity of generations as well as their progressive transformation in evolution;
- 4) *Developmental biology*; including growth, development, repair and reproduction of the individual;
- 5) *Regulatory biology*; dealing with the coordinating and integrating mechanisms, such as the nervous system, endocrines and homeostasis; and
- 6) *Group and environmental biology*; dealing with the relations of the individuals to one another and to their environment, including ecology, psychology, and sociology.

You will note that there is no longer any reference in this scheme to particular forms of life, but that every biological phenomenon can be defined in terms of one or more of these six categories. The value of such a system lies in the shift of emphasis from technical specialties to focal problems. Habitual communion, for instance, among all the different specialties studying the nervous system; or among all the different groups interested in growth, whether the growth of bacteria, plants, animals or human tumors, ought to result in more unified concepts than if the several lines were kept in segregation. In short, such schemes facilitate re-integration.

Striving for integration does not mean turning the individual investigator into a superficial jack-of-all-trades. It merely means to develop in him the urge to mind more than his own business so that he will compare and check and reexamine all he does in the light of what goes on elsewhere. For this purpose, critical surveys, as well as conferences and symposia, bringing together briefly

specialists from different areas, are of great help. Of even greater value would be a more extensive exchange of workers among different laboratories for longer periods. We then may overcome the factional isolation of teachers and investigators, and the narrow indoctrination of the students which stems from it.

A lot is being done in these days in the indicated sense; so much, in fact, that we must be on guard against stereotyped routine. Technical subjects have a way of self-propagation; witness the repetitiousness of conferences on adrenal hormones, nucleic acids, membrane potentials, radiophosphorus, or acetylcholine. Let us, therefore, try to keep the spotlight moving so that it will light into ever new sectors that need collaborative inspection and rethinking. Let us have more interdisciplinary fellowships for younger men to enable them to apply experience gained in one specialty to some different and new subject matter. Not only will such cross-fertilization give birth to new trains of thought, but the practice of crosslinking specialties will thus be openly encouraged. The wisdom of a fellowship program such as that endowed by Merck and Company at the National Research Council, which is specially dedicated to the promotion of interdisciplinary studies, deserves to be widely emulated.

Speaking of increasing specialization and division of labor, if we are to adjust to them with a minimum of duplications or omissions, we ought to have some clearer understanding on who is to assume what tasks. For instance, with their growing emphasis on the human individual, research and teaching in medicine are bound to concentrate on areas directly related to human health and ills. Reflected into pre-medical education, this will lead to greater preoccupation even in the more basic fields with man or mammals most closely resembling man's organization. Considering this trend, it becomes incumbent on the biological sciences as such to take increased responsibility for the more general aspects of bacteriology, cytology, histology, anatomy, physiology, biochemistry, and so forth. Indeed, much that is still traditionally considered the preserve of the medical school, could profitably be ceded to biology.

The biological sciences, in their turn, could do much more to give the budding medical student a firmer grounding for his later understanding of the machinery of the human body, its faculties and limitations. A standard course in embryology that is no more than an illustrated travelogue conducting the student through the changing scenery of the embryo by pointing to landmarks of ridges, craters and pipe lines, without telling him the how and why of the changes, is hardly the right introduction to the proper understanding of pathological phenomena of clinical concern, such as malformations, wound healing, regeneration, dystrophy, aging and neoplastic growth, all of which are but variants of what the normal embryo displays. Is it not high time to tell him more of our modern knowledge of the dynamics and mechanisms of embryonic processes and the causes of their deviations? Would he not get a better grasp of the vague concept of constitution by being shown more of the realistic background of genetics and ontogeny on which this constitution rests? Would he not become more adept at nerve repair if we explained just how nerves grow, are guided and connect? Would it not be good preparation for psychiatry to give him some biological

acquaintance with animal behavior, instinct and memory, so that he may better appreciate what is specifically human and what is not? Undoubtedly, by intelligent and cooperative planning, one could do a lot to make the pre-medical experience in biology more pertinent, adding not only to the perspective of the clinician but also to the orientation of the investigator who has come through this training.

Whichever way we phrase it, we come back to the human individual. This is the second plane on which we have to work. No organizational design becomes effective or defective save through the men and women who execute it. It may be sad that this needs emphasizing, but it does; particularly in view of some current illusions about the potentialities of so-called team work. No one familiar with the scientific process can share the hope that by hitching large numbers of scientists to a common treadmill, their aggregate effort will, by some sort of collective superintelligence, stamp out discoveries of staggering novelty. Discovery always takes shape in single brains. The building up of teams of workers of different training and viewpoints is a wonderful device to supplement, but not supplant, what only the individual mind and intellect can do—think. There is no substitute for human intelligence in science, so let us not act as if there were. If most of the riddles of life processes still lie obscure behind a closed door, let us not spend most of our efforts on ramming in that door by blind mass pressure, but rather let more people get busy with looking for the key or figuring out the combination of the lock.

To accomplish this, let us single out early those budding investigators who have native curiosity, imagination and drive and put them in their proper place in the front lines of exploration, before they are swallowed up by the mass channels of rote performance. They can be rescued from mediocrity, if we would only encourage them to assert leadership, productive scholarship and pioneering spirit; show them the virtue of taking calculated risks and make them sense the thrill of personal achievement; make them get pleasure out of effort and exertion, as in sports, and imbue them with the constant urge to probe for new directions, new objects, new techniques, but above all, new concepts and new insights gained by views taken from unusual angles. Cunning and daring must find favor again over sheer plodding, and critical self-direction take the place of drifting with the current.

Yet, at the same time, let us teach them the tolerance that goes with understanding; explain the workings of the scientific process which lives on all of these: methods, data, facts, conclusions, theories, hypotheses and concepts, all of them equally vital; restore a balanced attitude between the extremes of the pure fact finders and gadgeteers at one end, and the pure theorists and speculators at the other, and debunk the arrogance of their monopolistic claims; restore respect for systematic and unhurried work, and arouse suspicion of the flashy, but ill-supported, claim that trades passing notoriety for lasting truth; and raise that sense of responsibility and pitiless self-criticism without which even the best man is prone to go to seed.

Then, if we select the right young leaders and bring them up the right way

and show them the immenseness of yet unconquered problems full of the unknowns of biology, and if we have the courage to call these unknowns by their names, if we don't cover up our ignorance by pretentious words, if we phrase the problems as objectively and as precisely as a realistic approach to them would demand, if we present existing knowledge soberly and honestly without implying more than what we know or can legitimately extrapolate; in short, if we expose biology as challenging to the best of minds, then, I believe our progress is assured, and it will be balanced and steady. When I say we, I mean all those in education, administration, direction and support of research, with opportunities to detect and develop potential leaders.

This leaves out, of course, a large, and presumably the larger, fraction of the scientific population who have just average ability, not much originality, yet come to science with a will to serve. I am not talking of the ordinary laboratory technicians but of those who aspire to higher rank and a professional career in science. As competent specialists in limited areas, they are in increasing demand in industry, government positions, and as teachers, in institutions of higher learning. They are eminently useful, indeed indispensable, in what in military language would be called the mopping up and occupation duty and the logistic support of all the front lines. Just like the leaders, they end their formal training with a doctor's degree. Yet, this cannot conceal the fact that a true division of labor between the two groups is gradually emerging. The sooner we shall give official recognition to this fact and create a respectable status for the growing corps of needed technical specialists, the better for them and for the rest of our science. There is no reason why highclass technical experts in let us say electronmicroscopy, biostatistics, electronic recording, x-ray analysis, histochemistry, anthropometric measurements, assay of nutrients, and so on, who have neither a flair nor gift for original investigative work, should feel forced into it to make the grade of respectability, just because academic tradition has pronounced research as a virtue in itself. Such expert service personnel with Ph.D. degrees should be certified as valuable and full-fledged members of the scientific community with no explicit or implied pressure for research production. That class already exists in hospitals and some other institutions but it has not yet spread into the academic places where it is badly needed.

In general, the biological sciences are understaffed, both academically and technically. Increased recruitment is needed, from the high school level up. Such recruitment is, of course, up against a serious handicap—the inequity of the economic status of the academic profession. I do not want to go into statistics which would only boil down to the familiar comparison between the salaries of college professors and scrubbing women. The trend becomes the more alarming, the heavier the bid for scientific talent from industry, medical practice, and governmental agencies, all of which can afford to pay higher financial rewards for often less exacting services. True, the academic profession has always accepted financial loss in trade for a scholarly atmosphere. But this rationale is rapidly disappearing: Academic load grows heavier while industry and practice often provide attractive opportunities for scholarly activities. As the economic

gap widens, we may yet see a larger quota of high-grade research workers veer off from academic life, depleting the sources of scientific progress, at a time when they ought to be augmented. In realistic view, therefore, unless academic institutions can be secured against this drain, all the envisaged measures for assuring biological progress will come to naught.

Unless corrected, this trend could lead to a disastrous disruption of the structure of our science. This is a matter of national concern, hence, there are those who would look to government for relief. I would rather see help come through the growing realization of self-interest of those who benefit from the products of academic institutions. After all, much of the fundamental work on which industrial progress and medical practice rest comes from the universities and private research institutes, as a free gift to public wealfare. Considering the added service of training by which academic institutions mold human raw material into half-finished products at no cost to the consumers of such manpower, it becomes plain that more of the proceeds of these achievements will have to be plowed back into the academic process of teaching and investigation if the productive flow is to be maintained. Tax legislation allowing industry and the professions a larger tax-free share for contributions for educational and investigative purposes might act as stimulant.

As for the investigative process, however, the largest beneficiary is the public itself. Therefore, we must intensify the campaign to spread more widely true understanding of what the scientific process is, the good it does and what it needs. The public must be made to see that the acquisition of knowledge proceeds in a single coherent and continuous stream, which constantly delivers the stuffs that feed and shape our civilization. It yields them as naturally as a tree bears fruit if properly nurtured, irrigated and protected. But neither will a cut off branch bear fruit, nor can you grow fruit directly on the soil by short cuts. We must not tire of explaining this truth and illustrating it over and over again in order that the public may in due course learn how to invest its contributions to science most soundly and to best interest. We evidently do not promote such understanding by our publicity techniques which turn the spotlight merely on the recent fruits, many of them indeed unripe and sterile, while keeping the rest of the organic tree, which has produced them, unilluminated. If what they want is fruits, they must start with the seeds, the proper soil and climate, and tend the orchard.

This brings me to my conclusion. The biological sciences are one of the most profitable investments of society. To raise the efficiency of their yield to even higher quotas, we need further fundamental knowledge; hence, must strengthen the academic institutions that can get it. The public has a major stake in this, but is not quite prepared to understand and underwrite the riskier phases of the process. Meanwhile, progress basic to human welfare must not be held up waiting. Thus, pending public enlightenment, the next best thing to do is to have the trustees of public funds who know the story of scientific progress, or at least ought to know it, improvise proper measures.

The public, through taxes and annual collections, contributes a large share

to foundations and organizations supporting bio-medical research. Many of these foundations must be commended for the wisdom with which they allocate a part of the proceeds to the support of the basic biological sciences and their investigative program. But the very fact that they are explicitly commended, reveals a feeling that they are acting somehow "above the call of duty;" and that they have to justify to the uninitiated the propriety of such investment. Thus, they will obviously tend to stay at least as close to their specific practical objectives as they can reasonably do without betraying their basic faith in the need for the support of fundamental science. Unwittingly, they add to the mentioned tendency of premature grooving and freezing of our science into a few major channels at the expense of broad and unrestrained exploring; thus adding to the distortion, rather than to sound proportions, of our research pattern.

In order to correct this and to make public investment in bio-medicine more profitable, I would propose that all foundations, organizations and individuals who contribute financially to the advancement of medicine, assign a fixed fraction of their budgets, perhaps no more than 10 per cent, to a common pool for the promotion of the biological sciences as such, with no earmarks, no qualifications and no restrictions other than those of accepted accounting procedure. This pooled fund ought to constitute the risk capital of the biological sciences, to be used for exploration, prospecting and the support of the imaginative, critically controlled, but often unpredictable ventures into the unknown. It should be used as a mobile reserve for the support and encouragement of men with ideas, rather than of routine projects, and the rekindling of the dying flame of the curiosity and vision of the pioneer, which is the irreplaceable source of fundamental scientific progress and without which the scientific process is doomed to run down toward a thermodynamic death.

In 1951 alone about \$33,000,000 was spent on research grants in medical and allied fields, about two thirds from governmental and one third from private sources (1). If nine tenths were left wholly to the discretion of the donors, the tribute of one tenth, or \$3,000,000 annually, small as it is, would yet be the smartest bet on the advancement of the biological sciences, and through them of medicine, that one could place. The problems of education, research and economics are indissociable. What would be the use in arousing the appetite for adventure in our young scientists if then we starve them of the means to pursue their chosen courses? So let us not only put the spirit of risk back into the scientific process and make it respectable again, but also give it the necessary practical backing, if not by this, then by some other device.

This is a plea, but also a profession of my belief that something constructive will be done. And if so, none of the perils I have sketched will come to pass, and my evaluation here will have remained untested. Thus, at your bicentenary, this report may look singularly foolish. I hope it will, for this would prove that corrective measures had been taken in time to rescue biology from the precocious incursions of the law of diminishing returns.

Much of my comment applies to all modern science, but no other branch

stands to suffer so critically from its disregard as does biology. All of my comments can be documented by innumerable practical examples; but the cloak of anonymity seemed more appropriate to this festive occasion. One does not mar a family reunion by berating the black sheep. Moreover, in our family of biological sciences, all sheep are gray. One could not wash them white, just paint them darker; and I would rather be wrong than do this. For, I do feel a deep loyalty to this big family of biologists with its wonderful enthusiastic spirit and devotion to the ideals of scientific truth and service to mankind.

Yes, medicine must rest on a firm base of biology. But biology itself rests on a base in need of strengthening—the countless men and women, individuals all, who make it. May the next century give full scope to their creative, rather than merely imitative, powers, and all mankind will be the beneficiary. This is my birthday wish to you.

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1. DEIGNAN, STELLA LECHE AND MILLER, ESTHER: The Support of Research in Medical and Allied Fields for the Period 1946 through 1951. *Science*, 115: 321, 1952.

ERRATUM

In the article by J. A. Salzmänn and Stanley L. Wein on "Correlation of Dental Abnormalities in Hypo-Pituitarism", which appeared in the January-February 1953 issue of the *Journal of The Mount Sinai Hospital*, Volume XIX, Number 5, on page 672, the word "Left" should be "Right" on the first line of the legend of figure 4 and the word "Right" should be "Left" on the fourth line.

HEALTH, MEDICINE, AND ECONOMIC WELFARE

ELI GINZBERG, PH.D.*

When the Program Committee asked me to take part in this Symposium, I raised the question of the desirability of permitting an interloper from economics, even one who has long been interested in medicine, to participate. I hope that the Committee will not regret its judgment. I am very pleased indeed to be here.

On a commemorative occasion such as this it is conventional for speakers to stress past accomplishments and to dwell on the opportunity for continued progress. I have decided, however, to follow a different approach, even at the risk of impropriety, and to discuss certain fundamental relations between health, medicine, and economics which have been either ignored or minimized in the past, and to speculate about the import of these relations for the future.

It might appear from the propositions I have selected that I am not only an interloper but a dismal one. But economics was long known as the "dismal science" because it set itself the unpleasant task of explaining to well-meaning people that the world was too poor a place to permit them to accomplish all of their well-meaning objectives. Although the world today is not as poor as the nineteenth century economists believed, it is not nearly as rich as most social reformers assume it to be (1).

I have grouped the propositions which I plan to present around three headings—the economy, medical practice, and the larger society, which encompasses both the economy and medical practice, and much more. In each instance I will look backward and then forward. In the concluding section I will present a series of questions with import for public policy which seem to me to flow from these propositions.

THE ECONOMY

The marked improvements in the health of the population, measured in terms of greater longevity, lower morbidity, and greater effectiveness, largely reflect the rising standard of living which has characterized the United States and most of the Western world during the past many decades. This is not to deny the contribution made by medicine, including particularly the advances in public health, to raising this standard of living. Yet even kings who live in great splendor and riches cannot protect themselves from virulent disease if their subjects struggle in dire poverty. Nor is knowledge enough: China knows that the "honey carts" are the carriers of disease, but China cannot afford to do without human fertilizer.

The advance in the health of the West can be told in a few words: large-scale public works expenditures for the control of environmental sanitation; improved nutrition; the vast reduction in dangerous and injurious work; improved hous-

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ing. This does not mean, however, that all possible gains have been made, even in the United States. Far from it. The higher mortality and morbidity rates of certain handicapped groups and regions are so clearly related to a low standard of living that substantial gains in the health of these groups will surely follow increases in their income. A diversified and enriched diet will probably contribute more to the health of the population in the South than any specific addition to medical resources, such as an increase in the number of doctors or in the number of hospital beds.

It is exceedingly doubtful, however, that the gains made in the past can be duplicated in the future, unless, of course, we learn how to postpone death. We are probably past the optimum point. Increases in economic wealth may no longer lead to further improvements in mortality and morbidity rates. Ryle has called our attention to certain striking trends in Great Britain which indicate that it is no longer true that the poor always have the highest sickness rates and always die first. Diet, drink, and the pace of life have begun to take an excessive toll among the well-to-do (2). And in the United States due recognition has not been given to the fact that the greatest cause of premature death in the productive age groups is fatal accidents. Our ability to provide our youngsters with automobiles has much to do with the high death toll on the highways.

The same rapid economic growth that provided the population with the prerequisites for the maintenance of health had a large part to play in the rapid expansion of science and education, the foundation of modern medicine. In my opinion, only the experts have fully appreciated the extent to which most of the outstanding advances in health have been by-products of basic research in bacteriology, chemistry, physics, and the other sciences, rather than the results of clinical observation and experimentation. Moreover, it has not been fully recognized that only in a rich society can parents or parents-in-law underwrite a long course of medical training for aspiring doctors. Yet the improved level of medical care, particularly in the United States, has been greatly dependent on advances in medical education. And again, it is only in a rich society that universities and medical schools can contribute about two-thirds of the total costs of a medical education. The dependence of medicine on a sound economic base was brought home to me very clearly in 1929 during a year that I spent at Heidelberg. German medicine had never recovered from its setbacks during World War I and the inflation that followed. The British Health Service has yet to find an answer to the question of how it can prosper and progress in the face of a taut economy and a frozen national budget (3).

During the past few years there has been increasing concern in this country with the financial plight of medical schools and the funds available for medical research. Special efforts have been made and doubtless will continue to be made to increase public and private support. I would like to suggest that there is a serious danger of splintering the unity of higher education by concentrating on buttressing the foundations of medical education without regard to the ability of universities to support the humanities and the sciences. Medicine will be as strong or as weak as the foundations on which it rests and from which it must inevitably draw its major sustenance.

The relation between the economy at large and medicine in particular also suggests that the efficacy of therapy should be measured primarily in terms of the patient's ability, after treatment, to readjust to his environment. The test of recovery should be sought in the ability of a former patient to meet the economic and social demands of the society in which he lives. There is increasing recognition of this fact among physicians, who recognize that one cannot talk about effective therapy or cure except in terms of the individual's capacity to function. Our preoccupation with the building of tuberculosis sanatoria and our lack of concern with housing accommodations and employment opportunities for the patient with an arrested condition is but one of many illustrations of a medical structure focused on germs rather than on people. It is not reasonable, however, to look to medicine for the solution of such intricate problems of social functioning and adjustment.

Yet there is a danger of imbalance between the medical and social aspects of therapy. All too often society fails to reintegrate those who have been cured or whose illness has been arrested. When studying the hospital system of New York State some years ago, I was struck with the fact that in only one year had there been a decline in the census of mental patients. That occurred during the middle of World War II when peak employment conditions provided all marginal persons, including unstable individuals, with an opportunity for employment (4). Since the end of the war we have seen many commendable efforts to develop more treatment facilities for mental patients, the handicapped, and the aged. But many of these handicapped and chronically ill persons have more need for a job than for a doctor; a doctor will be able to do them little good unless they can find work. Unfortunately, our economy, despite its many achievements, has never been able to make effective use of the work potential of all its members.

MEDICAL PRACTICE

No matter what facet of medical practice is subjected to appraisal, the role of the physician is always the focus. The prestige of the physician has not always been high. As Dr. Ffrancgan Roberts points out in his remarkably incisive book on *the Cost of Health* (5), at Agincourt the surgeon ranked between shoemakers and washerwomen. Even at the end of the last century the surgeon did not have much prestige—he lost more than one out of every two serious cases. Roberts believes that the high point in the doctor's prestige was around 1920. At that time as an individual doctor he was able to exploit the new gifts of science and required little help from his colleagues and lay sources.

It may well be that the full impact on contemporary medicine, first of specialization and secondly of the growth of the auxiliary and semi-professional groups, has not been fully appreciated. In connection with the current studies of the National Manpower Council on scientific manpower, the Bureau of Labor Statistics recently prepared for us a table on the growth of the health professions. In 1920 there were slightly under 150,000 physicians and surgeons; today there are just over 200,000. The interesting comparison against which to measure this

relatively modest increase in the number of doctors is the total number in the health professions, which has grown during this period from slightly more than 450,000 to over 870,000 (6).

There are consequences that flow from this situation in which the individual practitioner has become more and more dependent both on his colleagues and on auxiliary workers. It seems unlikely that the prestige of the physician and his earning potentialities will remain unaffected by this technological change in the structure of medicine. At some point, the public, desirous of securing the maximum amount of medical care for the least expenditure, will ask why, as a matter of course, the assistant to the ophthalmologist does not do refractions; why a trained nurse, rather than the allergist, does not give the hay-fever victim an injection. Sooner or later these and related questions are sure to be put.

Another current assumption, that health is largely a function of the availability of medical care, and that medical care is largely a function of the number of available physicians, will likely be put to test and found wanting. In 1950 I testified before a Congressional Committee on a bill designed to consolidate all Federal medical and hospital activities into a single agency. The proponents argued that only in this manner could the civilian requirements for physicians in peacetime, and more particularly in war, be safeguarded, since competition among Federal agencies would result in inflating the total demand for physicians. In opposing this legislation on the ground that it would result in an administrative monstrosity, I called attention to the fact that although approximately 40 percent of the active doctors of the country were in the Federal service during World War II, it was impossible to find evidence of a deterioration in the level of health of the population. Such indices as were available pointed in the opposite direction. It is true that civilian doctors worked longer hours, and that they made greater use of hospitals to increase their effectiveness. But it is also true that there were more jobs available and that many people ate better. I did not try to convince the Committee that fewer doctors meant better health for the population, but I did question their presumption that more doctors automatically meant better health (7).

Aware of the dramatic contributions that the doctor can make to health, the public is giving increasing evidence of its belief that a democracy true to its name must make medical care available to all, irrespective of class or income. To some degree this attitude toward medicine long predates our contemporary democracy. Ever since the Middle Ages church and state have recognized some responsibility to provide medical services to those in need. In the past, these services for the needy involved, however, only a bed, food, and a minimum of nursing care. Today the provision of medical services for the indigent and for the much larger numbers who pay their way is a substantial economic undertaking involving an expenditure of more than \$10 billion a year, which is approximately 4 percent of the total outlay of consumers (8).

The concept that every individual should be able to secure all the essential medical services which he may require is easier to formulate than to accomplish. In fact it is questionable whether the proponents of this doctrine really under-

stand its full import. For instance, there is a marked difference between society's commitment to provide free education, even if the concept is expanded to include college, and a commitment to provide adequate medical care for all in need. Education can be quantitatively delimited. Moreover, it requires that the individual exert himself. The limits of medical care are much more elastic, and do not depend to the same degree on the active participation of the recipient of the service (9).

Although teachers have long since passed from the status of independent practitioners to civil servants or to employees of quasi-public institutions, the norm for doctors is still independent practice. This raises a host of serious questions, particularly at a time like the present when the public is becoming increasingly insistent that the advantage of medicine be made available to all and the medical profession insists that it must maintain its freedom to regulate itself. It is impossible to overlook certain consequences of this freedom, as, for instance, the disinclination of doctors to take up practice in the rural areas. And it is also discomfiting to hear a medical educator insist that it would be unwise to increase the number of graduates, for if competition among doctors should increase, they would simply resort to overdoctoring in order to provide themselves with the income they consider their due.

If we were a less pragmatic people, we would run into an insoluble dilemma of first defining medical care very broadly and insisting that it be made available to everyone in need, and at the same time be unwilling to assume the large-scale increases in expenditures involved and to countenance the marked restriction in freedom for doctors.

Another consequence of this high public evaluation of medical care is the conviction that only the best is good enough, and the best should be available to all. One need not be a psychologist to understand the strong emotional forces which drive many people to seek the best that money can buy when they or their families have need for medical care. But one need not be an economist to appreciate that this doctrine is certain to lead to waste and grief. In our world, where there are always more things that we want to do than we can afford, it is always desirable to practice economy at least to the extent of distinguishing between the essential and the desirable, and concentrating first on meeting the essentials. Several years ago I had an opportunity to visit Topeka, Kansas, where I was impressed by the variations in the average annual expenditures per mental patient in three different types of institutions. The state spent a niggardly amount, something less than \$300 per patient per year; the Veterans Administration was spending about \$2,000; the cost of a patient in the private institution, including analytic treatment, came to about \$10,000 a year. The wealthy may be entitled to spend their money as they see fit, but state and federal governments must have realistic guideposts. I was never able to find the answer to my question of what expenditure, considering all the other demands on government, gave the greatest promise of social gain.

Dr. Crohn, in his brief essay on the history of Mount Sinai Hospital, points out that in the first year of the hospital's operation total expenditures were

slightly in excess of \$5,000 for an estimated 15,000 days of patient care, or a per diem cost of approximately 30 cents (10). I was informed by the Director of the Hospital that this year the average inpatient per diem cost is approximately \$21 per day. Considering the fact that housing and personal service in the United States have always been relatively high-priced and considering further that so high a percentage of total hospital costs consists of housing and service, I feel that we have failed to give adequate attention to the best ways of economizing. Home care programs are a beginning, but only a beginning. During a visit to Japan some years ago, I was interested to learn that when a patient entered a hospital, his wife, mother, or sister came along to cook for him and nurse him. We may not be at a stage where hospital administrators would encourage families to install a camping stove in the corner of the room, but I believe that we are at the stage where we should make much more effective use of the nursing potential available in most families, possibly in the hospital and surely in the home.

One further illustration of the economics of hospital care. There has been much discussion over the past several years about the adequacy of our Veterans Administration hospital system and particularly about whether it should be expanded. After the war we built a large number of hospitals to care for the vastly increased number of veterans. We were so concerned about raising the level of medical care in veterans' hospitals that we gave inadequate consideration, in my opinion, to the probable changes in the future type of patient who would seek admission. Already there is evidence of a shift from general medicine and surgery and acute psychiatric conditions to a predominantly chronic population. Unless my reading of the evidence is wrong, the patient population of the future will consist mainly of men with stabilized disabilities, without family ties, who are more in search of a bed, food, and companionship than of medical care. At this point the principal need is for domiciliary homes, rather than hospitals (11).

That the Veterans Administration is not alone in its enthusiastic expansion of hospital facilities is proved by the extraordinary suggestion that emanated from many medical and hospital planners a few years ago, that each general hospital should add a substantial wing to care for chronically ill patients. In their understandable desire to have medicine pay more attention to chronic illness, these experts overlooked the questionable economics of seeking to have government or voluntary groups take on the excessive expenditures of caring for a large number of chronic patients within general hospitals. Here, as elsewhere, the real challenge is how to get necessary medical attention to as many people as require it in the least expensive manner possible. This would hardly be accomplished by building accommodations for them in general hospitals (12).

SOCIETY

This brings me to a consideration of certain broad social attitudes and values that play so large a part in determining the medical objectives which we set ourselves and the extent to which we are striving to meet these objectives. We place a very high value on human life, at least most of the time—evidence of

the exceptions is in our homicide and accident rates. I am not sure that we fully appreciate the implications of the rapid advance of medical science in a society committed to the prolongation of life. We are now able to save from early death many whose congenital defects will doom them to a life of severe limitations. Much more important are the developments at the other end of the age scale, in the contributions of modern surgery and the antibiotics to the prolongation of the life of the aged. No one who has ever had an opportunity to walk through the wards of one of our state mental hospitals and has seen the thousands of bedridden patients suffering from senile dementia and cerebral arteriosclerosis can fail to be restive under the question of whether the ability of these patients to survive an attack of pneumonia by virtue of the new antibiotics is a boon to themselves or society.

A second attitude which permeates so much of the public's thinking about the right of every individual to essential medical care derives from the conviction that all illness is an act of God. Support for this attitude is found in the fact that even the strictest adherence to the rules of health is no protection whatever against such serious illnesses as cancer, diseases of the blood, arthritis, degenerative lesions of the nervous system, and many others.

Yet it is difficult to ignore completely the issue of personal responsibility in the maintenance of health and the avoidance of many types of illness. There are those who play hard and are willing to take large risks; there are those, who although not hypochondriacal, place a high value on being cautious in matters of health. We frequently overlook the fact that good medical care can be provided only to those who have the desire and the intelligence—not to mention the means—to seek it. Moreover, in this age in which the “unconscious” has come into its own, it is no longer possible to ignore the tremendous potentialities that many individuals find in the exploitation of illness. In her study of the *Cost of Medical Care* in the San Francisco area, Emily Huntington called attention to a series of cases requiring very expensive treatment for conditions described under such terms as “nervousness” or “nervous breakdown.” Clearly, emotional disturbances must be considered as illnesses. The interesting conclusion that is suggested by Huntington's material is the greater occasion that women had to seek medical attention for these illnesses, which is perhaps a reflection of the fact that they did not have as much support from routine work as did their husbands. Moreover, some probably were “exploiting” their illness in a search for secondary gains (13).

Modern medicine, which has reached the height of achievement in restoring to life all but two out of every hundred men wounded on the field of battle, has great reason to be proud of its accomplishments. Similar illustrations could be offered from civilian experience, from saving the premature baby to the further prolongation of the life of the octogenarian. But the great advances of science and the medical applications thereof have set a new stage. Increasingly, medical practice must struggle with more intractable problems, with the prolongation of the lives of individuals who are long past their productive powers and whose failing strengths make it more and more difficult for them to cope with their

environment. The tremendous concern of modern medicine with individuals suffering from emotional difficulties frequently compounded by somatic complaints is resulting in a shift from the biologically specific to the uncharted and treacherous regions of the moral and the social. And again, the very logic of its own advance is forcing medicine to devote much effort to the kindly support, but very limited alleviation, that it can offer those who have had the misfortune to be stricken by a disease for which science has not yet found an answer. Unless the span of adult life is substantially increased, it is questionable whether the medicine of tomorrow can be as productive as the medicine of yesterday. More and more people can anticipate reaching old age with only a fleeting acquaintance with the physician.

PUBLIC POLICY

What are the major implications for public policy which flow from this analysis? There are many more problems currently in the realm of public debate than could possibly be outlined here, but a few can be summarized. What are the major unmet needs of the American public for medical care? How many and what type of resources are required to meet these needs? What methods of organizing and paying for medical care can yield the greatest net benefit?

What have been the major unconventional, possibly dismal, propositions that I have reviewed that bear on the foregoing policy issues? In summary, these were my major contentions: The great improvements in the health of the public during the past century, although dependent in part upon the development of science and the medical applications thereof, were largely a result of general economic and social advances. The economic basis of contemporary medicine is not sound; witness the unsatisfactory status of medical education. There has been a general over-evaluation of clinical medicine and a failure to recognize that medicine is increasingly preoccupied with the more intractable problems—those related to congenital defects, degenerative diseases, and mental illness—in which its major contribution to the patient is supportive and ameliorative rather than curative. This fact has great bearing on the future of the physician, whose status and income will probably decline as he finds himself unable to practice independently and is forced to associate himself with the auxiliary branches. I also pointed out that no matter what miracles modern medicine can perform, many patients require other types of assistance, such as an opportunity to work. In addition, insufficient attention has been paid to keeping the costs of medical care within bounds, which is a very important consideration in light of the strong demand for more and better medical care.

It would not only be unconventional, but foolish, to deny that large sectors of the population do not now have adequate medical care. However, the expansion of medical care is not the certain answer to better health. We have seen that major challenges lie in the area where medicine is severely restricted, if not presently impotent. Many challenges also lie in the area in which the purely medical becomes intertwined with the economic and the social, as in the case of the need of the handicapped for jobs, the need of the chronically ill for homes,

the need of the mentally ill for a protective environment. There are some sick people who could become well if they could obtain good medical care. But there are many more who have long been sick and who will remain sick because, unfortunately, medicine can do little or nothing to aid them. The American public must begin to appreciate the wide gap between its aspirations for better health and the ability of modern medicine to provide it.

Informed persons have long recognized that the quantity and quality of medical care could not be substantially increased unless there were a prior, or at least a simultaneous, increase in medical personnel and medical facilities. Included in my unconventional propositions were several that bear directly on this issue of expanding medical resources. There is no simple relation between the number of doctors and the level of the community's health. Further, increasing the number of doctors does not mean that doctors will practice where they are needed most. To increase the number of hospital beds is no solution if individuals or the community are unable or refuse to maintain them adequately. Too little attention has been paid to the record of state and local governments in providing mental, tuberculosis, and general hospital care. It is a record that hardly justifies much optimism about the results to be anticipated from a large-scale expansion of medical facilities supported by tax funds.

The issue that is most frequently joined in public relates to the deficiencies that currently exist in the methods of organizing and paying for medical care. Insurance plans that include payment for both hospital costs and professional services at a reasonable cost that enable self-supporting citizens to provide for catastrophic illness cannot yet be secured in many parts of the country. There are many reasons for this, not the least of which has been the lack of effective leadership by the medical profession itself. But those who expect great progress to be made by changing the present methods of payment overlook the fact that some of the worst deficiencies in the provision of medical care relate to the sector where government has been paying the bills. Further, they relate to that twilight zone between medicine and other social resources required for effective functioning, i.e., income, housing, work, which are again far beyond the purview of any insurance scheme, private or public.

If maximum benefit for minimum cost is established as the criterion, there are certainly serious deficiencies in the present organization of medical services. But it would take an extreme proponent of the unique value of medical care to argue that nothing counts but maximum social efficiency in the organization of medical services. Freedom of choice of a profession; freedom of choice of a location for practice; freedom of choice of a physician—all these and other freedoms are more than political slogans!

There is also a real need for cost consciousness throughout the entire medical structure; and the public is entitled to protection against undue exploitation with respect to professional fees. But once again one must guard against over-optimism from structural changes. Medical care is expensive and it will remain expensive. The only real control over costs is to keep the amount of medical services within bounds; to be sure that essential needs are met but that medical services do not expand beyond.

Medical care is a means to an end, never an end in itself. It is the obligation of the medical profession to remind itself, and to remind the public, that disease, injury, and death, are embedded in life itself and that medicine has the goal of alleviating suffering and contributing to the renewed effectiveness of the sick and injured. It dare not promise emotional and physical health for all, for this would be unrealistic.

In attempting to meet the challenge which I set for myself at the outset of raising important if largely neglected issues of the relations between health, medicine, and economic welfare I have covered too much ground too quickly. Yet the basic propositions appear to me to be very simple. Heredity and economic well-being, rather than medical care, is the key to health. The economic base of modern medical care is not firm: the financing of medical education, the economics of medical practice, the payment for medical care, all leave much to be desired. Paradoxically, the very advance of medicine is reducing the sphere of its potential productiveness: the physician is increasingly concerned with older persons who are afflicted with conditions for which science has as yet no answer.

In conquering one source of human unhappiness, medicine will doubtless find itself face to face with yet another. Society can profit greatly from the strengths of medicine but it must remember that it is health that it seeks. But health, though dependent in considerable part on medicine, also has deep roots—in biology, religion, and economics.

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MEDICINE AND THE COMMUNITY: THE ROLE OF THE VOLUNTARY HOSPITAL IN COMMUNITY MEDICAL CARE

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To acquaint you with the changing functional relationships of voluntary hospitals to the communities which they were designed to serve, I must lead you on a tour extending over more than a century. Perhaps in this manner, I may help you to understand the new and more complex problems of present-day medicine as I see them.

Before the beginning of the nineteenth century, hospitals were intended for the sick and the dying who sought refuge within their walls because they had nowhere else to go. The hospital was then analogous to the poorhouse where the aged, the infirm, and the destitute sought shelter and protection from the world. Like poorhouses and orphan asylums, the early hospitals were established largely by religious orders. Only later did local governments begin to recognize their responsibility to erect and maintain public hospitals with local tax funds for the benefit of the indigent.

In the eastern sections of this country the concept has persisted to this day that the existence of governmental hospitals does not absolve voluntary agencies from a share of the responsibility for the medical care of the indigent. We still hold it to be the American way to provide help for our neighbors in time of sickness and misfortune and not to leave them wholly to government. In accordance with this ancient tradition, the extensive system of voluntary hospitals in the United States continues to be supported largely by religious and similar philanthropic interests.

RECENT DECLINE IN NUMBER OF WARD SERVICE BEDS

The flowering of the voluntary hospital system in the United States during the nineteenth century was also due in part to the fact that early in our industrial era the philanthropic contributors, the people of means in the community, began to appreciate the need for hospital beds as private accommodations in time of sickness for themselves, their families, and their friends. In the East, this came as an afterthought; in the more recently settled regions of the middle and far West the desire for private accommodations was the primary reason for the establishment of most voluntary hospitals in those sections of the country. This motive was so prevalent in these regions that many of the voluntary hospitals, except those which are part of medical schools, have only a token number of service beds. Even in our century-old hospitals on the eastern seaboard there has recently been a growing tendency to look to municipal institutions supported out of general tax funds for the care of the indigent sick. In New York City and some other communities, partial reimbursement of voluntary institutions from public funds for the hospital care of some of the indigent has undoubtedly retarded this trend. Now, because of current economic pres-

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tures, private philanthropy is gradually but regretfully abandoning to government its former share of responsibility for the hospital care of the medically indigent.

Mount Sinai Hospital and some of the other large hospitals in this city remain among the notable exceptions. The ward service accommodations still constitute about 56 per cent of Mount Sinai's total bed capacity. Unlike many of the other 85 voluntary hospitals in New York City, its admission policy for the ward services does not permit the exclusion of any patient because he or she cannot afford to pay anything toward the cost. Admission to the wards is still based solely on medical need.

Yet, even at Mount Sinai Hospital almost all beds that have been added to the institution during the last thirty years or more have been built for private patients. The only recent exception has been 33 ward beds in the new obstetrical pavilion out of a total of 154, and these are so designed that they may be used as low-cost private facilities. In 1942, Mount Sinai Hospital had 530 ward beds; by 1952, the number had been reduced to 488, a reduction which is not yet of serious consequence. Most other voluntary hospitals in New York City have had a greater proportionate decline in ward beds than Mount Sinai. During the last decade the total number of ward service beds in the voluntary hospitals of New York City declined by more than 1700. Among those that remain, many are often used for private patients of individual doctors. Meanwhile during these ten years, the ward beds in the municipal general hospitals increased by almost the same number and they are occupied at times up to 110 per cent of their capacity.

It is therefore evident that even in the East the trustees of most voluntary hospitals are being gradually obliged to abandon the concept of "sweet charity" which motivated their forebears in the nineteenth century and are slowly contracting their hospitals' services to the care of persons who collectively can pay the full cost. In New York State, the law no longer requires a voluntary hospital to maintain ward service beds in order to gain tax exemption. Any hospital can secure designation as a voluntary institution and obtain tax exemption if it is operated without profit.

In this respect, some voluntary hospitals are coming to resemble proprietary hospitals, the essential difference being that the former are operated for the benefit of the community under a trusteeship whereas the proprietary institutions are operated by owners for their personal profit. The trustees of the voluntary hospitals usually provide some facilities in their institutions for medical education so as to maintain standards of medical care, whereas the owners of the proprietary hospitals, being more interested in profits, rarely indulge in this costly luxury. As they provide little or no educational opportunities, proprietary hospitals are obliged to hire some resident physicians at a salary. But even this distinction is diminishing, for increasing numbers of small and even medium sized voluntary hospitals are also no longer able to secure interns and residents because of the absence of service beds which are essential for the training of young physicians.

INFLUENCE OF HEALTH INSURANCE PLANS ON WARD SERVICES OF
VOLUNTARY HOSPITALS

This trend to abandon to government the care of those who cannot pay the cost of hospitalization would greatly accelerate the movement to medical care in governmentally administered institutions for a large segment of our population, were it not for the phenomenally rapid growth in this country of voluntary hospital and medical insurance plans, notably Blue Cross. The Blue Cross movement was begun in 1929 for the benefit of the employees and students of an educational institution, Baylor University in Dallas, Texas. It extended to Essex County, New Jersey, and then to New York City in 1935. The extraordinarily rapid spread of hospital and medical care insurance throughout the United States in the succeeding years has been due largely to the increasing demands of wage earners that they be not left to charity or become the recipients of public assistance when they are ill. The growing public appreciation of hospital and medical care insurance has now made it one of the major fringe benefits in collective bargaining by labor unions. Many far-sighted employers are providing it voluntarily for employees and their families as an additional guarantee of their economic security.

Prepayment both for hospital and for medical care under voluntary non-governmental auspices is creating a revolutionary change in present-day financing of hospital and medical services. Some form of hospital or medical care insurance or both is now carried in this country by 86,000,000 people. Blue Cross in New York City (the Associated Hospital Service) alone has over 5,000,000 subscribers. More than 3,500,000 persons in this city are also insured under a variety of medical insurance plans against doctors' bills for medical services rendered to them in a hospital. It is amazing that this phenomenal change in the financing of hospitals, the assumption of hospital operating costs by the general public itself, with proportionately decreasing aid from private philanthropy, has occurred within the short space of 10 or 15 years.

At first, hospital insurance, especially Blue Cross, was purchased chiefly by people of medium income. During the last 7 or 8 years, it has been extending rapidly to those in the lowest income brackets, who previously used the ward accommodations. This insurance factor, more than the intentional exclusion of the medically indigent, is now responsible for the present low rate of occupancy of ward beds in voluntary hospitals in New York City, which in 1951 averaged 74 per cent, one hospital reaching an extreme low of 21 per cent. At the same time, municipal hospitals are filled throughout the year beyond their capacity.* A continued downward trend in the occupancy of service beds in voluntary hospitals is to be anticipated until, in the not too distant future, the major, if not the entire, responsibility for the hospital care of persons who cannot through insurance or otherwise pay the minimal cost of hospitalization will be largely concentrated in hospitals maintained by local, state, and federal governments.

* Many people who carry hospital insurance find their way into municipal hospitals for a variety of reasons. In 1951, the Blue Cross (AHS) alone paid the City of New York more than \$1,600,000 for their hospital care.

INFLUENCE OF HEALTH INSURANCE PLANS ON MEDICAL EDUCATION AND RESEARCH

A distinguished President of the American Hospital Association, Dr. Anthony J. J. Rourke, recently pointed out that the teaching and research functions of our voluntary hospitals are succumbing slowly but surely to the effects of prepayment for hospital and medical care. On August 13, 1952, Dr. Rourke warned the President's Commission on the Health Needs of the Nation in no uncertain terms that the existing medical teaching services of hospitals would disappear as the prepayment plans continued to divest teaching hospitals of their service cases. He said, "One of the most serious problems created by the prepayment movement has been its effect in markedly decreasing the clinical material on the teaching services throughout the country. Some other way will have to be found for training the doctors of tomorrow."

Voluntary hospital insurance plans will continue to spread until they cover almost the entire population, as will medical care insurance to meet doctors' bills. This means that the beds of our voluntary hospitals which now belong to the staff as a group are on the way out, unless a special effort is made through a new device to retain them under these changing conditions. As a sign of the times, several of the largest and oldest voluntary hospitals in New York, including Mount Sinai, have recently begun to convert some of their ward facilities to semiprivate use.

We must face the issue whether the voluntary hospitals of this country are to become merely hotels for the private patients of individual doctors. It cannot be too strongly emphasized that this is a matter of utmost importance to all people in the community, even to those who may never be obliged to enter a hospital, for it will seriously affect the future quality of medical care which they receive.

The modern American hospital is or should be the cornerstone of community medical practice. It is not generally realized that 90 per cent of private medical practice is conducted outside of hospitals, in peoples' homes, in doctors' offices, in diagnostic and x-ray laboratories.* The quality of medical care in the community depends not alone upon the calibre of undergraduate education in the medical schools but perhaps even more upon the educational environment in the hospitals to which young doctors are subsequently exposed during the important formative years of their internship and residency training. Because of the extraordinary speed of scientific progress, the educational influence of the hospital upon the practicing physicians of the area must also continue thereafter throughout the remainder of their lives.

THE SOLUTION OF THE PROBLEM

It is my purpose in this Centennial address to point out that the foremost challenge confronting the better voluntary hospitals under these changing conditions is to devise means to continue programs of medical education and re-

* This is the recorded experience of the Health Insurance Plan of Greater New York on a completely insured population to whom medical, laboratory, x-ray, and other clinical services are available without financial barriers to adequate utilization.

search within their institutions when all patients are able to meet the costs of hospital and medical care either directly or through prepayment plans. Without such activities within a hospital, the quality of its medical care cannot be maintained. Some hospitals already without service beds borrow some of the private patients of individual staff members for general teaching purposes. Interns and residents find this a most unsatisfactory educational experience compared with the educational and research opportunities in hospitals which maintain an active clinical service. For intern and residency training, there is no educational substitute for service beds occupied by patients of the clinical service. Sporadic or even periodic lectures for the edification of the visiting staff and of community physicians are also totally inadequate substitutes for service beds occupied by patients who are the joint responsibility of the staff of a clinical service.

The President of the American Hospital Association, in calling attention to the urgent need for action, did not describe what the voluntary hospitals must do to preserve their past functions as community centers for medical education and research under the changing order. I submit that a way has been found, if voluntary hospitals will take advantage of it.

Heretofore, ward service beds have been used by patients who paid nothing for their medical care even though some may have been able to pay part of the cost of their hospital care. Non-paying patients on the clinical service of the hospital are traditionally cared for by the medical staff as service cases because they are not private patients of individual doctors and there is no direct financial obligation between a patient and a doctor. Such service cases have always been accepted as the professional responsibility of the doctors of the service as a group under the direction of the chief of the service—in other words, they are cared for through ideal group practice. Why change this traditional form of group practice merely because some of the former ward patients now prepay their medical care?

If voluntary hospitals are to retain their clinical services as more and more of the former free ward patients prepay their medical as well as hospital care, all that is necessary is that the staff of the hospital as a group accept the responsibility for a limited number of insured persons who prefer to be cared for by the staff as its joint responsibility. Many well-known group practice clinics throughout the country have demonstrated that this system of practice can promote high quality of medical care and maintain high educational standards.

The payments received for the medical care of these insured people are then pooled for the benefit of all the doctors belonging to the medical service group and distributed equitably to them in proportion to the time which each member devotes to his general hospital duties and his relative skills and years of experience. Any imputation that this involves the corporate practice of medicine by the hospital can be avoided if the medical group receives all of the distributable income.

Quite naturally, any change in the methods of medical practice or in the remuneration of physicians for their services, no matter how urgently needed because of the changing conditions in medicine or on how limited a scale, will

arouse fear among the timid that it may destroy private practice. To allay this unwarranted fear, it should be understood that the avowed purpose of the hospital is to retain the existing methods of group practice on a limited number of service patients. Members of the hospital staff who do not wish to participate in group practice may continue to care for their private patients independently in private or semiprivate beds. But in view of the trend of the times and the onrushing changes in medical economics, private group practice by a part of the hospital's staff cannot be avoided if the important educational functions of voluntary hospitals are to be preserved. This is no more "socialistic" than are the 700 or more group practice diagnostic clinics which have long been in successful operation throughout the country.

GROUP PRACTICE IN HOSPITAL DIAGNOSTIC CLINICS AND CONSULTATION SERVICES

The younger members of the staff at the Mount Sinai Hospital may not realize it but they have in fact been engaged in the private group practice of medicine for more than 20 years—in the Hospital's "Consultation Service for People of Moderate Means." This Service was inaugurated by the Hospital in 1931 for the benefit of the community outside its walls in spite of strong opposition by many members of its own medical staff and the objections of the local medical society. It took much courage at that time to establish a diagnostic service operated by the staff of the Hospital as a group practice unit. The majority of the medical profession felt that diagnostic services even on patients referred by general practitioners should be rendered only by individual specialists practicing as soloists. It was held that a voluntary hospital had no right to encourage its staff to practice as a group in competition with individual specialists, even for the benefit of people of moderate means.

Within a few years after its establishment, the Consultation Service was universally accepted by the staff of the Hospital as a most valuable community asset. In more recent years it has even been officially endorsed by the county medical society and unqualifiedly recommended for adoption by other institutions. Today it is one of the community services for which the Hospital is known throughout the country and in which it takes great pride.

The director of the American College of Surgeons, Major General Paul R. Hawley, and other medical leaders such as Dr. Paul Magnuson have recently advocated the establishment of similar diagnostic centers at qualified hospitals to be operated by the hospitals' medical staff as group practice enterprises for the benefit of the general practitioners of the community and their patients. Such diagnostic clinics serve to raise the level of medical practice in a community because of the resulting economies of group practice and the increased efficiency of a medical group which is at liberty to use all the physical resources, professional knowledge, and technical skills of a modern hospital in solving the diagnostic problems of the sick. The question has been posed whether the establishment of an out-patient diagnostic service for ambulatory patients referred by individual physicians is as far as a hospital staff should go in group practice.

Experience has demonstrated that diagnostic clinics or consultation services

operated solely for referred patients on a fee-for-service basis do not meet the total needs of medicine in the changing order. During the past 20 years, the Consultation Service at the Mount Sinai Hospital, and similar hospital diagnostic clinics, have proved to have only limited value as educational centers. Ambulatory patients are referred by practicing physicians to the Consultation Service for an episode of illness, the diagnostic investigation is completed within a brief period, and the patient is then lost to the Service. As a means of training interns and residents and for the other educational and research requirements of a hospital, a Consultation Service or diagnostic clinic is not a substitute for the indoor clinical services of the hospital.

GROUP PRACTICE ON HOSPITAL INDOOR SERVICES

The teaching services of voluntary hospitals can be preserved through the wider application of medical group practice to indoor patients. Staff members who practice group medicine on private patients in the ambulatory service of a hospital can, as a group, provide medical care, both diagnostic and therapeutic, for similar patients occupying hospital beds. This has long been done at Billings Hospital in Chicago, Ford Hospital in Detroit, the Hitchcock Clinic at Hanover, New Hampshire, Harper Hospital in Cleveland, Pratt Diagnostic and Baker Memorial in Boston, and other hospitals which are organized for indoor as well as outdoor group practice. The patients are cared for by the combined staff as service patients under the immediate direction of the chief of the medical or other service to which they are admitted. These institutions maintain exceptionally high standards of medical care and provide superior training facilities for young physicians.

When confronted with resistance to change, trustees of voluntary hospitals and leaders of philanthropic agencies which support hospitals should be reminded of a similar situation which confronted the medical schools of this country a little over 100 years ago. At that time, many medical schools were used by members of their faculties for their own financial aggrandizement. Under these conditions undergraduate medical education could not keep pace with the advances in the medical sciences. Yet the professional resistance to change seemed for a long time almost insurmountable. The situation confronting medical education at that time was not significantly modified until after the complete reorganization of undergraduate teaching at the medical school of the University of Michigan in 1869, the establishment of a new modern medical school at the Johns Hopkins University in 1893, and subsequently a nationwide critical survey of medical education by Abraham Flexner.

Today, we face an equally important crisis in regard to the education of physicians after they leave the medical school. Voluntary hospitals must reorganize at least part of their staff to meet the changing order if they are to fulfill their community responsibilities, other than the mere provision of beds and facilities for private patients of individual doctors.

COMPREHENSIVE MEDICAL CARE THROUGH PREPAID GROUP PRACTICE

If the service beds of the hospital are to be retained in order to promote teaching and research and maintain the present high standards of medical practice within the institution, some of these beds should be assigned to a medical service group of the hospital responsible for the total care of insured patients on a prepaid comprehensive basis. Persons who are insured under medical expense indemnity plans which pay on a fee-for-service basis are not completely satisfactory for admission to these facilities because of the limited coverage which these plans provide. The fee-for-service method of remunerating individual doctors within the sharp limitations of these plans makes it difficult, if not impossible, to treat them as service cases. No such difficulty is encountered when insurance provides comprehensive coverage through prepaid group practice.

An insurance plan which provides comprehensive medical care enables people of low or moderate income to budget all the annual costs of medical care for themselves and their families. Such families face no financial barriers to early and prompt utilization of medical, x-ray, and laboratory services. The per capita income derived from their premiums goes to the medical group which has accepted the responsibility for their total medical care. All the professional and technical facilities of the medical group are promptly available for early diagnosis and treatment, on both an ambulatory and in-hospital basis. Under these circumstances, preventive medicine and early disease detection become the primary objective of the responsible medical group.

Now that the communicable diseases of childhood have been largely conquered and we are faced with the mounting health burdens of an aging population, the most important public health problem of our day has become the prevention and early detection of disease at a stage when it can still be cured or arrested. Only through such measures as part of a total health program can the incidence of chronic illness and prolonged disability be held in check and the load on our hospitals be reduced. Hospitals cannot remain aloof from this most pressing problem of our time, for they house the complete facilities and the best staff with which to meet the challenge.

People of low and moderate income, who constitute the great bulk of our population, can only secure the benefits of modern preventive medicine and early disease detection under a system of prepaid comprehensive medical care. Under such a voluntary system of prepayment, there are no financial barriers to early and adequate utilization of medical services for early disease detection and therapy. It has now been amply demonstrated in more than 100 communities throughout the country that it is professionally feasible and financially practical to provide such complete care through prepaid group practice in return for annual premiums which people of low and moderate income can afford to pay out of their tight budgets, with or without the assistance of their employers. Today, about 3,000,000 people are receiving comprehensive medical care through such prepaid medical groups, almost 400,000 in New York City alone.

INTEGRATING THE HOSPITAL INTO THE PUBLIC HEALTH RESOURCES OF
THE COMMUNITY

The time has arrived when the voluntary hospitals should take a more positive approach to this problem if we are to avoid governmental intervention in the field of medical care. Hospital beds are expensive to build and to maintain. Under comprehensive medical care insurance, many beds can be saved by the organized medical service group of the hospital, which can carry out the maximum amount of diagnostic and therapeutic procedures on an ambulatory basis. The people of this country cannot long continue to meet the mounting costs of hospital and medical care; this is one effective way to reduce these costs.

Another significant contribution of great community value which challenges the hospital involves the integration of family physicians with the hospital's professional and technical resources. Family doctors who provide more than 60 per cent of all professional services are being increasingly isolated from the main stream of medical science. They should be brought back into the orbit of the hospital both for their educational benefit and in order to relate the hospital more intimately with the medical and socio-medical problems of the community. A hospital's medical group which provides comprehensive medical care to insured persons in the community requires a large number of family doctors on its staff for services to insured families in their homes, in doctors' offices near their homes, as well as in the hospital. Such family doctors are essential members of the hospital group. They enjoy all the educational advantages of an intimate hospital relationship. Through them, the medical care provided by the hospital's group for the insured is personalized and continuing.

From their personal family doctor, whom they originally selected from the roster of the medical group, the insured families can obtain preventive health services and, through him, all the laboratory facilities and consultation services of the hospital are made available to them whenever required. Because of the continuing relationship of the family doctors and the hospital group, environmental, occupational, and other social factors which produce illness become the vital concern of the participating physicians of the hospital, and measures for their correction become part of their daily responsibilities. This is in sharp contrast with the current preoccupation of hospital physicians with episodes of advanced illness. Because of the continuing concern of the hospital's medical group with family welfare, preventive psychiatry can be brought back into medical practice and become part of the total services for family care.

In the preceding paragraphs I have endeavored to indicate the manner in which the voluntary hospital can recreate the educational, scientific, and social environment in which to train the idealistic young physicians of tomorrow for modern medical practice—for service in the hospital and in the homes of the people. By this means, the voluntary hospital can maintain its rightful place as an integral part of the public health resources of the community.

Few trustees or supporters of hospitals have as yet grasped the future implications of the rapidly changing order of medicine and of the changing methods of hospital financing upon the future quality of medical practice. As business men,

bankers, or lawyers, they cannot be expected to keep abreast of the march of time in medicine. Physicians on the visiting medical staffs of hospitals are absorbed in their individual private practices and are rarely concerned with their hospital's community relationship. Being individualists by training and inclination, most doctors are glad to utilize as many beds as possible for their revenue-producing private patients. To those responsible for the operation of hospitals, the administrators and trustees, more private beds mean more revenue to the institution and less need for the troublesome collection of philanthropic funds to meet annual deficits in the hospital's operating budget. The trustees, the administrators, and the professional staffs of most voluntary hospitals all have good reason to develop the same "blind spot" in their field of vision.

I end this Centennial address on a note of provocative interrogation. Are our voluntary hospitals to be gradually transformed by rising medical costs and the spread of prepayment into hotels for the patients of individual doctors? As it moves into its second century, the Mount Sinai Hospital, its trustees and its staff, cannot be content to rest upon past laurels and daily contemplate with complete satisfaction these magnificent buildings which are the monuments to the great educational and scientific endeavors of our forebears. They are an ever-present symbol and a challenge.

A CENTURY OF MILITARY MEDICINE

MAJOR GENERAL GEORGE E. ARMSTRONG*

It is a great pleasure for me to participate in the observance of Mount Sinai's Centennial. The country as a whole owes much to the great progress in hospitalization in the past one hundred years. Great centers like Mount Sinai have been the setting for many of the advances in medicine in modern times.

We in the military have a special interest in the progress of hospitalization, for we lean heavily on the great civilian institutions of this country for aid and counsel in maintaining high standards in our own hospitals. The importance of these standards can hardly be overemphasized, for it was only two centuries ago that the great military medical historian, Sir John Pringle, indicted the hospitals of that period as being the single greatest factor in high battlefield mortality. After facing the hazards of front-line duty, today's soldier may look forward to the best treatment and hospitalization obtainable. For the reversal of Pringle's indictment and the role that military hospitals fill today in assuring rapid recovery and complete rehabilitation, we must acknowledge our collective indebtedness not only to the practitioner of military medicine, but also to the great and progressive hospitals of the United States.

Before we discuss the status of military medicine during the past century, it might be well to consider its meaning.

Military medicine is certainly not a new medical specialty. There are those, in fact, who contend that it is the oldest. Their premise is based upon the superstitious nature of early man and his faculty for blaming diseases on the intervention of evil spirits. Consequently, only disorders which were demonstrably man-made, such as the thrust of a spear, were considered proper fields for mortal "tinkering". Thus, within this narrow field of permissible practice arose the military surgeon and, ultimately, modern medicine.

Military medicine also has unique problems. Probably no group of physicians, with the possible exception of the Rockefeller Foundation staff, must concern itself with so many bizarre diseases in so many out-of-the-way corners of the world as do the medical services of our armed forces. With the possible exception of Civil Defense, no medical group must face the problems of treatment and evacuation of mass casualties that are constantly with the Army Medical Service. Probably few civilian physicians have the problem, so common in military medicine, of guarding the health of large numbers of men in highly varied sanitary and climatic environments.

Despite all of this, however, military medicine is no especially compartmentalized form of practice foreign to civilian medicine. It employs the same specialists, the same basic techniques, possibly adapted to meet special situations, as does its civilian counterpart. Malaria, for example, has been a serious military medical problem since it was first identified. Yet today, except in degree, it is equally the problem of the public health officer and the civilian

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internist, and the advances in prevention and treatment are equally valid in military or civilian practice. Similarly, the front-line military orthopedist may encounter a different variety of cases than his civilian confrere, but his techniques are still essentially the same.

How, then, may we define military medicine? If we consider the primary mission of the Army Medical Service we have the basis for an acceptable definition: Medicine practiced in a military setting to conserve the fighting strength and to maintain the health and physical well-being of our troops.

Military medicine is consequently a synthesis of all elements of medical practice and specialization. Many of its great contributors have spent their entire careers in uniform; others have temporarily donned the uniform under the stress of national emergency; still others have never been in uniform but have made their contributions in the laboratory, ward and clinic.

Like civilian hospitals, the progress of military medicine in the past century has been nothing short of phenomenal. I propose to discuss the nature of this progress under four headings, all of which are interrelated. They are: first, the advance of medical knowledge; second, the growth of medical logistical support; third, the increase of understanding and cooperation by nonmedical military authority; and fourth, the establishment of close liaison with civilian medicine.

Unquestionably, the general advance of medical knowledge in the period we are discussing has been the most important single factor in the progress of military medicine, for the zeal and heroism of the military medical officer avail him little if he lacks adequate means to prevent, treat, or cure human ailments. This is particularly true in the case of disease.

To compare the conditions of 1852 with those of the present, we need to cite a few statistics. Let us first consider the setting of 100 years ago as it applied to military medicine in the United States.

For the United States Army, 1852 was a nominally peaceful year. Its 9,000 men were stationed in a hundred far-flung frontier posts, many of them guarding the trails for the thousands of emigrants heading for Oregon and California. The danger from attack was relatively slight, but the hazards of disease were always present. During the year, admissions to Army hospitals, excluding injuries and wounds, were about 2,500 per 1,000 men, a rate about five times that of disease admissions in the Army last year, *including* Korea. From the standpoint of mortality, the contrast is even more amazing. About two and one-quarter per cent of the Army died of disease in 1852; one-twentieth of one percent in 1951. Thus, the chances of dying of disease 100 years ago were .45 times higher than today.

This, however, is only a small part of the story. If we go four or five more years into the past, we find that in the Mexican War the annual mortality rate from disease was ten percent and that about 11,000 of a total force of 100,500 died of disease. Nor is the picture appreciably changed, if we advance to the War Between the States. Here we have an annual disease mortality rate of seven percent. For the Spanish-American War in 1898, the death rate from disease was two and one-half percent. For World War I, the death rate had declined to one

and seven-tenths per cent, and by World War II it had fallen to six one-thousandths of one per cent, approximately the present level.

It need hardly be emphasized that while some of these deaths occurred because of poor organization and others because of plain stupidity, the great majority were due to widespread ignorance of the nature of disease and its prevention. For example, yellow fever and dysentery constituted two of the important causes of death in the Mexican War, yet the origin of these diseases was not clearly understood until the turn of the century. In the Spanish-American War, typhoid fever caused sixty per cent of all disease deaths. Although the role of polluted water was already understood, it was not until well after the end of the war that the role of the carrier was determined, and not until 1909 that a vaccine against typhoid was available.

Today, these particular conditions have largely disappeared, not only as a threat to the lives of our troops but also as a serious problem in maintaining military effectiveness. The incidence rate for dysentery for the entire Army in 1951, for example, despite conditions in Korea, was less than one and one-half per thousand troops per annum. Typhoid fever had been reduced to a microscopic admission factor of seven one-thousandths of one case per 1,000 troops per annum. There were no cases of yellow fever reported in 1951.

Many principles that we today take for granted were completely unrecognized as late as 1875. In that year the Surgeon General of the Army published what was then a highly progressive "Report on the Hygiene of the United States Army", prepared by John S. Billings, later to become the first professor of military hygiene in the Army Medical School. It pointed out a number of existing deficiencies. There was, for example, the question of air space in barracks. Billings pointed out that persistent odors were due both to overcrowding and poor ventilation. He urged that bathrooms be provided so that men could bathe in the winter as well as in the summer. He criticized the ration which, because of lack of fresh vegetables, had been responsible for 632 cases of scurvy between 1868 and 1874.

But, significantly enough, he had nothing to say about water purification, food-borne infections, insects or general causes of disease. This may be understood when we remember that at the International Medical Congress in Philadelphia in 1876, a paper on "The Present Evidence concerning 'Disease Germs'" concluded that the real causes of these diseases (referring to hospital gangrene, cholera, typhoid, relapsing fevers, and many others) were unknown.

This, then, is the effect of expanded medical knowledge. Once the cause of the disease is known, its substantial elimination is usually only a matter of a comparatively short time. Then we concentrate on more effective cures for those cases that break through our preventive measures.

Our success, however, should not lull us into a feeling of complacency. Take, for example, the case of World War I. Until September of 1918, the Army's disease mortality rate was amazing by any previous criterion—only one-half of one per cent per year. Then came the great world pandemic of influenza that struck civilians and soldiers alike, but particularly the latter in their crowded

cantonments. Between September and November of that year, there were 316,000 cases of influenza and 54,000 cases of pneumonia among troops in this country. By the middle of October, the *weekly* death rate from influenza and pneumonia had approached the previous *annual* rate for all causes and, for the entire war period, these diseases had been responsible for about seventy-five per cent of all disease deaths. This is significant, I believe, because, even with the more effective protective and therapeutic measures we have today, it would be a bold man who would predict unequivocally that it could not happen again.

What has been true of disease, of course, has been equally true in other branches of military medicine. The development of new surgical techniques, advances in anesthesia, the virtual elimination of gas gangrene and tetanus, and the more forward utilization of whole blood and plasma, as well as many other factors, have had a dramatic effect in reducing the suffering of the battle casualty, in greatly increasing his chances of survival and in assuring him a more rapid and complete rehabilitation.

Statistics from the War Between the States indicate that thirteen of every hundred wounded who reached medical attention died; in World War I, this percentage declined to eight; in World War II, to four and one-half; and now in Korea to a phenomenal two and four-tenths per cent. These are dramatic evidences of the advancement of medical knowledge.

There is one facet of military medicine which has almost no civilian connotation. This is the study of wound ballistics. The medical services have long acknowledged their responsibility to maintain a soldier's health and to restore him if he lives long enough after being wounded to reach medical attention. They have not heretofore been able to provide any effective protection to the man so seriously wounded as to be unable to reach medical attention, and who must consequently be classified as "killed in action".

Today, this is not the case. A medical team in Korea studied the type and location of missiles in 4,600 cases of wounded, and 1,500 cases killed in action. As a consequence, where we once thought body armor was too heavy and bulky to be worn in combat, our whole concept has now changed, and we have collaborated with the Navy on a laminated plastic vest which has proven highly promising in early tests in Korea.

The subject offers extremely good possibilities for the future. The "killed in action" is still beyond the assistance of military medicine, but if protection will transfer him into the "wounded in action" category, or perhaps prevent the wounding altogether, then at least we will have made a frontal assault on the "killed in action" column which has shown no substantial change in the last few years. Deaths from disease and deaths from wounds have both collapsed under the pressure of medical advancement. Let us hope the "killed in actions" will be next!

The dictionary defines logistics as "that branch of military art which embraces the details of the transport, quartering and supply of troops in military operations." As far as military medicine is concerned, improvements in this field have constituted a major contribution toward more effective medical care.

This is not difficult to understand. In the Mexican War, medical supplies themselves were usually in reasonable supply, however, all of them were standard drugs, instruments and the like, and none had been devised exclusively for field use. Likewise, both the transportation and storage of such supplies were dependent entirely upon the ingenuity of the medical officer concerned. Consequently, even when supplies of medicinals were adequate, there was still little equipment on hand of value in establishing even the crudest field hospital. To complicate matters further in this campaign, no tentage was provided. Thus, even the most primitive protection for the sick and wounded was lacking. Finally, there were no ambulances, and casualties could be evacuated only on the jolting, springless supply wagons of the period. Transportation of this type was a serious threat to the well-being of even the healthiest man; it frequently was fatal to the seriously ill or wounded.

In such a setting, there would have been many fatalities even if medical knowledge had reached today's high level; but it was to be many years before the Army was to adopt permanent improvements. It was not until almost ten years after the close of the Mexican War, for example, that the first ambulance was tested, and the two-wheeled models adopted at that time proved so completely ineffective that they were rapidly "lost" by units to which they were assigned early in the War Between the States. The support of the medical service early in that war was little better than that in the Mexican War. Medical supplies were poorly designed for field use, tentage and other field hospital accommodations were still largely lacking, and transportation was still entirely inadequate for both medical supplies and casualties. The delivery of medical supplies was largely improvised, and in many cases the personal attention of a medical officer was necessary to assure delivery of a shipment to the proper place at the proper time. The result was that too many medical officers found themselves without even the barest equipment and too many patients found themselves either entirely without care, or bounced in jolting wagons or box cars to entirely inadequate hospitals located in homes or churches. The records of the period show that many deaths were actually due to exposure to cold or rain, and that many others could be charged to starvation, because at best the field ration consisted of hardtack and bully beef. At other times the troops had no food at all for periods of many days.

It is to Jonathan Letterman that the Army Medical Service is indebted for the first practical system for the evacuation of wounded. He also established the first centralized ambulance units and planned a network of more fully equipped and properly located field hospitals. If the gradual adoption of his plan throughout the Army did not result in the ideal, it did represent a startling advance for that time, and a vast decrease in the pain and suffering experienced previously by our troops.

Unhappily, the Spanish-American War brought no further advance in the logistical phase of military medicine. Previous lessons had been largely forgotten when the campaigns in Cuba, Puerto Rico and the Philippines began and the result was the same complete failure to make necessary provision for the sick and wounded that had marked earlier military operations.

By World War I, however, the first modern concept of medical logistics had appeared and since that time there has been steady and continuous improvement. In Korea today, there are a number of factors which in themselves are matters of logistics, but which assure the maximum dividends from advances in medical knowledge.

This has been particularly marked in the evacuation of patients. The use of helicopters for the front-line transportation of the seriously wounded is one well-publicized example. Still another is the large-scale use of aircraft for the evacuation of patients from Korea to Japan and from Japan to the United States. Although not in themselves new, the early shipment of special hospital train cars to Korea and the provision of busses that can be converted to evacuate casualties by rail are typical of the painstaking logistical support that has become part of our present-day operations.

Other advances are reflected in the elaborate hospital system, which extends from the forward Mobile Army Surgical Hospitals in Korea to the permanent-type hospitals in Japan and the United States.

Then, too, the military surgeon is no longer dependent on standard-type equipment which all too often proves entirely inadequate for field operations. Today, under the guidance of a unified military medical agency, great improvements have been made over even World War II equipment. Recent additions include a new portable X-ray machine, a new field operating table and new lightweight medical supply chests—to mention but a few.

Our medical supply system worked admirably during World War II, and it is working even more effectively today. Through a network of supply depots, operated by medical service personnel, we have been able to assure an adequate flow of medical supplies to the front lines of Korea at all times, and have maintained sufficient flexibility to substitute new drugs for old, once their value is established.

One of the fields in which considerable, although unheralded, progress in military medicine has been made is in greater cooperation between the officers and men of the line, and their medical personnel.

History reveals numerous examples of how commanders failed to heed the advice of their medical officers and, as a consequence, paid fearful prices in terms of human life. There have been a number of reasons for these tragic errors in judgment.

Rarely has disdain by commanders for the welfare of their troops been one of them. Probably most of them would have agreed with the philosophy of the Byzantine Emperor Leo, who said, early in the tenth century: "Give all the care you possibly can to your wounded, for if you neglect them you will make your soldiers timorous and cowardly before a battle, and not only that, but your personnel, whom you might preserve and retain by proper consideration for their health and welfare, will be otherwise lost to you through your own negligence."

The fact remains, however, that on many occasions in the past commanders have incurred unnecessary casualties through either failing to ask for the advice of their medical officers, or failing to heed it, once given. One consideration was certainly the backwardness of medical knowledge during most of the last century.

Many commanders unquestionably thought that their years of service in the field were of more value than the uncertain judgment of their surgeons.

Until World War I, the limitation in staff organization was also a factor. Decisions were largely the personal decisions of the commander, made with a minimum of technical counsel. Consequently, the medical officer often remained unheard, or found himself proffering unsolicited advice.

Thus, the change when it came was due to the growing competency of the medical officer to give sound advice, the recognition by commanders that their medical officers could actually reduce the hazards of the campaign, and the emergence of large staffs to handle the increasingly complicated details of modern warfare.

I believe one word of warning is appropriate here. I am not suggesting that the existence of numerous casualties is in itself a reflection of poor judgment on the part of the commander, or ineffectiveness on the part of his surgeon. The first objective of a field commander must always be the achievement of his tactical mission. Thus, many World War II battles were fought in such highly unhealthy places as New Guinea, Guadalcanal, Burma, and North Africa, although no medical officer—nor commander either, as far as that is concerned—would recommend any of these as ideal locations for disease-free campaigns. That they were reluctantly chosen was due obviously to considerations of strategy and tactics. Korea certainly falls into this category. With all the dangers from disease and the problems of evacuation inherent in that country, we are fighting there because that is where the fighting began.

However, today the inclusion of medical planning on all levels of command is a great weapon in the successful application of the principles of military medicine. Increasingly, since the onset of World War I, plans for military operations contain carefully-detailed medical annexes, and medical officers are consulted before the final decision is made in either tactics or strategy. Even when the capabilities of an actual or a potential enemy are analyzed, the medical officer's verdict on disease or evacuation problems is weighed equally with such factors as strength and firepower.

And while today's commanders are increasingly concerned with the implications of military medicine, the same can be said of their troops.

In the early days, when the sole protection of a command against an epidemic was to march from one location to another, there was little necessity for a soldier to concern himself greatly about principles of disease protection. With the advent of sound principles of preventive medicine, it became not only desirable, but also essential that he should so concern himself. As these principles have become more effective and more complicated, the role of the individual has become more important.

Korea provides a fresh example of how effective can be the intelligent participation of the individual soldier. The low incidence of dysentery and diarrhea, in an area where the pollution of water is so general, may be attributed to a number of factors, but certainly the troops deserve special credit in observing individual water purification procedures. Similarly, the low incidence of malaria in Korea

reflects the conscientious manner in which the troops there have been utilizing the drugs supplied to them.

This has been an area of gradual advance. To expect men voluntarily to swallow pills and adhere to the innumerable rules of personal hygiene and individual protection is asking a great deal of human nature. But we have found that the response to these protective measures can be amazingly good when troops are both well trained, well disciplined, and well informed.

A final, but by no means the least important, element in the advancement of military medicine has been the increased liaison and cooperation with civilian medicine.

Two things in the past, particularly in the latter part of the nineteenth century, largely prevented such cooperative effort: geography, and the lack of any great surge in medical research. As far as geography was concerned, the very location of our frontier garrisons effectively isolated most of our military medical officers from their civilian colleagues, even though at the same time they assumed responsibility for most of the medical care of the thousands of emigrants heading westward.

The great stride in medical advancement toward the end of the century, accompanied by the gradual assignment of such officers as George Sternberg, Walter Reed, Bailey K. Ashford, Frederick Russell and others, to posts where they could engage in medical research, marked the beginnings of a new day. The contributions of these men to civil health problems and the parallel contributions of their civilian colleagues to military problems cemented a relationship that has grown ever closer with the years.

Today, through such agencies as the National Research Council, the Research and Development Board of the Department of Defense, and the Armed Forces Epidemiological Board, a high level of cooperation and coordination is maintained. From a practical standpoint this means that overlapping research has been largely eliminated, and that investigative work may be done in military research facilities, by other governmental agencies by civilian research centers, or by all three working in active collaboration.

Primaquine is a good example of this type of teamwork. Original work on this drug, which shows great promise as a cure for vivax malaria, was done largely by leading civilian researchers under the supervision of the U. S. Public Health Service. When primaquine reached the stage where it showed military possibilities, the Army took over the major role in its study, but with the continuing aid of the Public Health Service and the same civilian scientists.

With the epochal advances of the past century, what remains to be done? What are some of the unsolved problems of military medicine?

Much depends on mankind itself. If our civilization advances to the point where war disappears as a method for solving international grievances, we may anticipate the disappearance of armies, navies and air forces, and the consequent honorable retirement of our military medical services. However, today, this dream seems far away and many problems press for solution.

I believe the practice of medicine calls for a special measure of humility

because each advance of medical knowledge seems to uncover new mysteries that must be faced in turn. Certainly this is true of military medicine.

Our greatest victories in military medicine have been in our battles with disease, but these battles are far from ended. In dealing with the pestilences which our armed forces have encountered in the past 100 years, we have eliminated the vectors of some, immunized against others, and successfully treated most of the remainder. In many cases, we have accomplished all three, but there are still too many areas where protection can be provided only at a single point in the path of the disease.

Consequently, amazing as our health record is in Korea and many other primitive areas, disease rates are still higher than in the United States. This differential presents an obvious challenge, a challenge that can be met only by forging an even better armor against infection.

Then too, we still have "blind spots" in our medical knowledge. Like our civilian colleagues, we still are relatively defenseless against the respiratory diseases which are the single greatest cause for admissions to military hospitals. As a consequence of our World War II experience and subsequent experience in Germany and Korea, we recognize that we know all too little about infectious hepatitis—its cause, prevention and treatment. Similarly, in Korea today, we find ourselves facing a relatively unknown disease in acute hemorrhagic fever, about which world medicine knows little and which American troops have never encountered in the past.

In the field of trauma, there are likewise many problems remaining. We know, for example, how much the forward use of whole blood may contribute to the favorable prognosis of a battle casualty. Yet despite the great strides made between World War II and the present time, we are still inhibited by whole blood's short usable life, the special packing it needs in transit, and the controlled refrigeration it needs in storage. We have not yet solved the problem of treating that frequent sequel to shock, lower nephron nephrosis. Then, too, although the past winter has demonstrated the effects of proper clothing and troop discipline on the incidence of cold injuries, much remains to be done before we can consider that we have a completely effective protection.

The field of military psychiatry has made great strides during the past 10 years, but here again much remains to be done. As our manpower resources become more critical, we must have better answers as to the best use of our sub-marginal groups. On the battlefield, we must have more effective means of preventing psychiatric breakdowns.

I could go on with these examples. Those I have cited are simply typical and do not demonstrate their relative importance. Neither are they an acknowledgment of failure. They do, however, emphasize that we should not be too quick to scorn our colleagues of the past century. Today's unsolved problems pose a challenge that must and will be met by the medical profession—civilian and military alike.

Before much could be done about history's major scourges, it was necessary to discover basic causes. Until this was accomplished, these earlier medical officers

did the best they could, even uselessly attempting to substitute personal heroism and industry for knowledge. Colonel Ashburn, in his history of the Army Medical Department, perhaps expressed it best when he said, "If much that was thought and done then is now considered folly, we may know that much which we think and do will be folly in its turn. All that goes with the seed was the same then as now, and if we can use it as well in the light of day as our fathers used it in theirs, we shall not have done badly".

Work on many of our unsolved problems is well under way in the hospitals and great research laboratories of our country. Some of these research projects are being carried on in military installations; others, financed from our military medical research budgets, are being investigated by other departments of the government, by the great research foundations of this country, and by individual researchers in civilian medical centers. Thus, we resolutely continue our march up a path toward an eventual goal of elimination of suffering and disability. It is a goal which we shall not attain in our generation nor in many generations to come; but when Mount Sinai commemorates its Bicentennial, we hope that our successors will be able to report much progress toward the ultimate solution of our problems.

In the meantime, I anticipate a continuation of challenging and highly gratifying years for all those who seek to contribute to society through medicine — be it military or civilian.

PUBLIC HEALTH, 1852-1952

LEONARD A. SCHEELE, M.D.*

On a bleak November evening in 1921, a spry young man of 98 years rose to address an audience of cheering colleagues in the Grand Ballroom of the Astor Hotel in this city. Stephen Smith, great pioneer in public health, chief architect of New York City's Metropolitan Health Law, co-founder and first president of the American Public Health Association, had come, as guest of honor, to celebrate the fiftieth anniversary of the professional society he had fathered. And because he possessed so much more to command veneration than the accustomed charm and humility of advanced age, I think that what he had to say about anniversaries and longevity is appropriate—to this occasion and to my topic.

"The wise and prudent man regards anniversaries", said Stephen Smith, "as beacon lights which illumine his future pathway and enable him to avoid its pitfalls and seize the fleeting moments of success. So let us on this most auspicious anniversary look backward and learn the lessons of experience which it teaches before we take a step into the uncharted future." (1)

Few of our generation and still fewer of Stephen Smith's could take as long a look backward as he. What he saw, from the watchtower of nearly 100 years of life, was the ever-changing picture of man's struggle for health and longevity.

"From time immemorial, 'old people' have been asked the secret of their lives which has enabled them to live so long", he reminded his audience. "The folly of this question is seen in the variety of answers given", he concluded. For Stephen Smith had seen—had lived—society's transition from the secret of longevity to the science of longevity. He had seen an end of "the long period, unnumbered centuries, of ignorance and superstition as to the conditions affecting the public health, which promote or prevent longevity." So, on the basis of scientific principles developed within his lifetime, Stephen Smith proclaimed one hundred years "the birthright of every child born fully developed". And he bade his colleagues to press on their fight so that when the association would celebrate its centennial in 1971 deaths would be "limited to those afflicted with old age, or to disease or accidents unpreventable and incurable by any agencies known to science" (2). Stephen Smith's present-day colleagues still pursue that goal.

PUBLIC HEALTH ORIGINS

The story of public health throughout this hospital's century of service, reduced to its simplest terms, is the story of how society has responded to the challenge of sickness and sudden death. Viewed in these terms, public health is not the death-rate itself nor the sanitary condition of any specific time or place. Rather it is the basic institution created and maintained by society to do something about the death-rate and the sanitary conditions and many other matters related to life and health.

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When Mt. Sinai hospital of New York City opened its doors to the sick poor in 1852, public health as a social function was just beginning to emerge from the experience of urban communities, chiefly in the northern countries of Europe and the Western Hemisphere. That experience presented many sharp challenges.

In the first half of the nineteenth century, industrial expansion for the first time outstripped both the scientific and institutional capacities of society to deal with its social consequences. There had always been industry and commerce—but never before with such rapid mechanization, change in methods of organization, and increase in operations. There had always been cities—but never before had their population doubled, even tripled, in a decade or less. There had always been epidemics, sickness, and death—but never before were the opportunities so great for the rapid spread of disease, never before the populations at risk so large, never before the effects upon a nation's economy so crippling. While England, France, Germany, Belgium, Holland, Switzerland and other European nations grappled with these problems, the United States was experiencing both the political and economic growing pains of a young nation.

In this environment, Mt. Sinai Hospital and hundreds more of our great voluntary institutions were born. In this environment, the functions of public health were hammered out in the fire of necessity. The fuel was a compound of common sense, civic responsibility, humanitarian impulse, intellectual curiosity, and a few pinches of science. For it must be remembered that a hundred years ago, medicine had relatively little science to bestow upon this hospital or public health. Indeed, it had few effective agents for cure—still fewer for prevention—in its empirical armament.

In every age, men are bound to work out a systematic expression of their social aims which is related to the existing knowledge, the particular needs, and the climate of opinion then prevalent. The great pioneers of the modern public health movement have performed this indispensable task from early in the nineteenth century down to our own day.

The early formulations of modern public health theory and practice were seldom the work of one man; but the names of Chadwick, Southwood Smith, and Simon in England, and of Shattuck and Stephen Smith in America still shine like beacons for the public health professions. The importance of the classic reports with which these men are associated lies not so much in the originality of the ideas expressed as in the fact that they reported conscientiously the facts, brought together the experience of enlightened persons of their time, and were influential in persuading others to profit by the lessons of experience.

Stephen Smith came down to New York City to complete his medical education in 1850. That year, the Report of the Sanitary Commission of Massachusetts by Lemuel Shattuck and others was issued. Smith's sanitary survey of New York City appeared fifteen years later. These reports, descending from the work of Chadwick and his contemporaries, contain—if any documents contain—the charter of public health in the United States.

In his foreword to the 1948 facsimile edition of the Shattuck report, Professor C.-E. A. Winslow says:

"Surely, this is an astounding document for the year 1850 and it has its

message for us. . . . I know of no single document in the history of [public health] science quite so remarkable in its clarity and completeness and in its vision of the future." (3)

The reports of Chadwick, Shattuck, and Smith are far from obscure. Their ideas spring out of facts known in the day-to-day lives of individuals and communities. Their proposals seek to meet expressed and unexpressed needs of men, women, and children in the deepest of human experiences. Even before this country had made any organized efforts for prevention, we find in Shattuck's report not merely a narrow plan for dealing with emergencies, but a fully developed philosophy of public health.

Enriched and extended by a century of scientific progress and practical experience in our changing society, the philosophy of Shattuck remains the philosophy and purpose of the public health profession today: "We believe

. . . that the conditions of perfect health, either public or personal are seldom or never attained though attainable;

. . . that the average length of human life may be very much extended and its physical power greatly augmented;

. . . that in every year thousands of lives are lost which might have been saved;

. . . that tens of thousands of cases of sickness occur, which might have been prevented;

. . . that a vast amount of unnecessarily impaired health, and physical debility exists among those not actually confined by sickness;

. . . that these preventable evils require an enormous expenditure and loss of money and impose upon the people unnumbered and immeasurable calamities, pecuniary, social, physical, mental, and moral, which might be avoided;

. . . that means exist, within our reach, for their mitigation or removal; and

. . . that measures for prevention will effect infinitely more than remedies for the cure of disease." (4)

Let us then examine public health as it functioned in the United States a hundred years ago and as it functions today. In doing so we shall focus on certain factors which brought about significant changes in this century-long process, and note trends toward new changes. In this general framework, I shall discuss first some of the scientific and social changes over the past 100 years; second, the structure of public health; and third, public health practice.

SCIENTIFIC AND SOCIAL CHANGES

As an integral part of the total social fabric, public health changes in relation to scientific progress in its particular field and in the general technology. Likewise, it changes in relation to changes in the economy, and the social and political attitudes of our nation.

The discovery of the germ causation of disease in the last quarter of the Nineteenth Century, with the subsequent rapid development of bacteriology, immunology, and related disciplines is one of the most glorious contributions of science to the health of mankind in all ages. Bacteriology confirmed the belief

of the public health pioneers that prevention can be a concrete achievement, rather than an abstract ideal. It has enabled public health literally to transform the world (Fig. 1).

These and many other communicable diseases have receded under the combination of control of environmental hazards and protection of the individual through immunization, chemotherapy, and other types of prevention and treatment. Even down to our own time, some of the major advances in chemistry and chemotherapy have contributed more to the control of communicable diseases than to that of other disease categories.

A century of progress in the preservation and distribution of foods, together with the birth of nutritional science and its application, has made another major contribution to human health. Advances in these fields illustrate the inter-relation of basic science and general technology with public health progress. Agricultural, manufacturing, and medical discoveries have created whole new industries, at the same time vastly increasing the consumption of nutritious foods, improving the average diet, and virtually eliminating such wide-spread diseases as pellagra, endemic goiter, and rickets.

Stephen Smith told his 1921 audience an anecdote which illustrates this amazing improvement in human nutrition. "The average housewife today knows more about diet than did the whole medical profession fifty years ago", he said. And he proved this by the story of a wealthy young American of the 1850's who journeyed all the way to London to consult a world-famous specialist about his chronic dyspepsia. When the consultation was over the young man said, "But Doctor, what can I eat?" "How do I know", the specialist answered. "Only you and God Almighty know what you can eat!"

As the pioneers of public health so clearly recognized and demonstrated, both problems and progress in human health are interrelated with problems and progress in the total social environment. As Shattuck and Smith were concerned with the effects of industrial expansion, the growth of cities, housing, shifts in population, and the general standard of living, so today these elements of a great industrial civilization aid in the improvement of the nation's health and at the same time contribute to the problems which must be solved.

The results of the many advances in the biological sciences, and changes in the technological and social fabric are evident in our longer life expectancy (Fig. 2), our aging population (Fig. 3), and our major contemporary health problems (Fig. 4).

THE STRUCTURE OF PUBLIC HEALTH

The structure of public health in 1850 had little resemblance to that of today. Shattuck states in his report that "The condition of perfect public health requires such laws and regulations as will secure to man associated in society the same sanitary enjoyments that he would have as an isolated individual; and as will protect him from injury from any influences connected with his locality, his dwellinghouse, his occupation, or those of his associates or neighbors, or from any other social causes. It is under the control of public authority and

Reduction in death rate Selected infectious diseases, 1900-1950

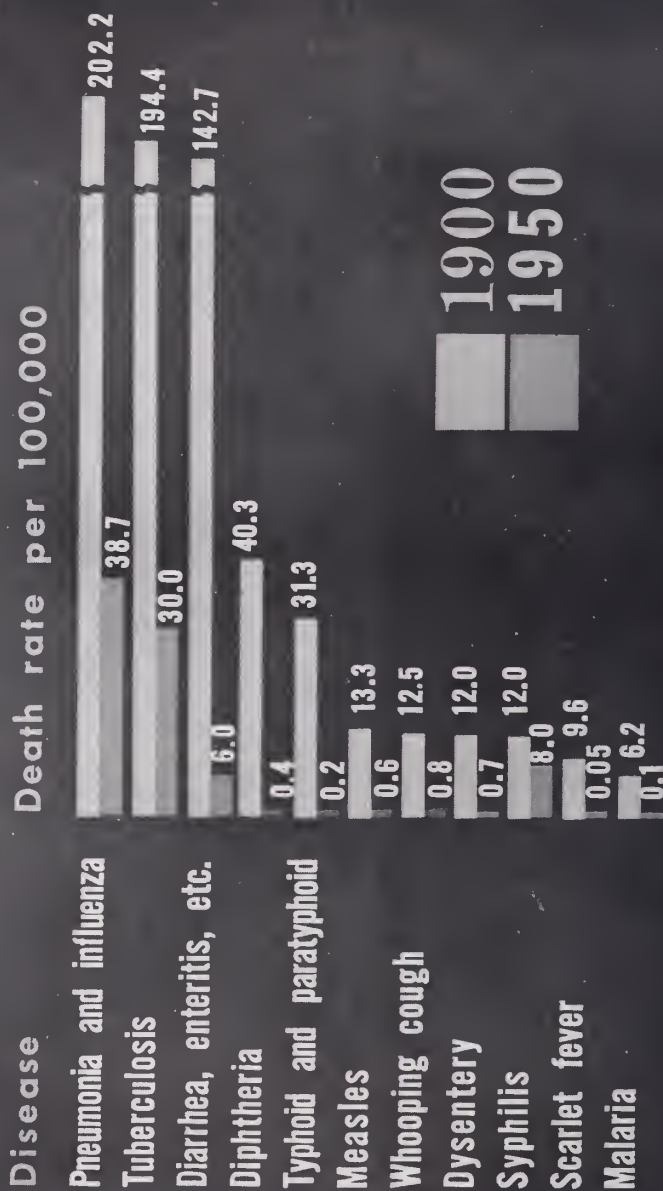


FIG. 1.

Our longer life expectancy

67.8
yrs.



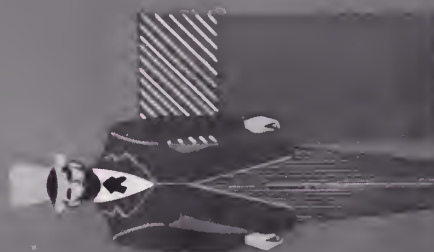
1950

49.2
yrs.



1900

40 yrs.
30 yrs.



1850

FIG. 2.

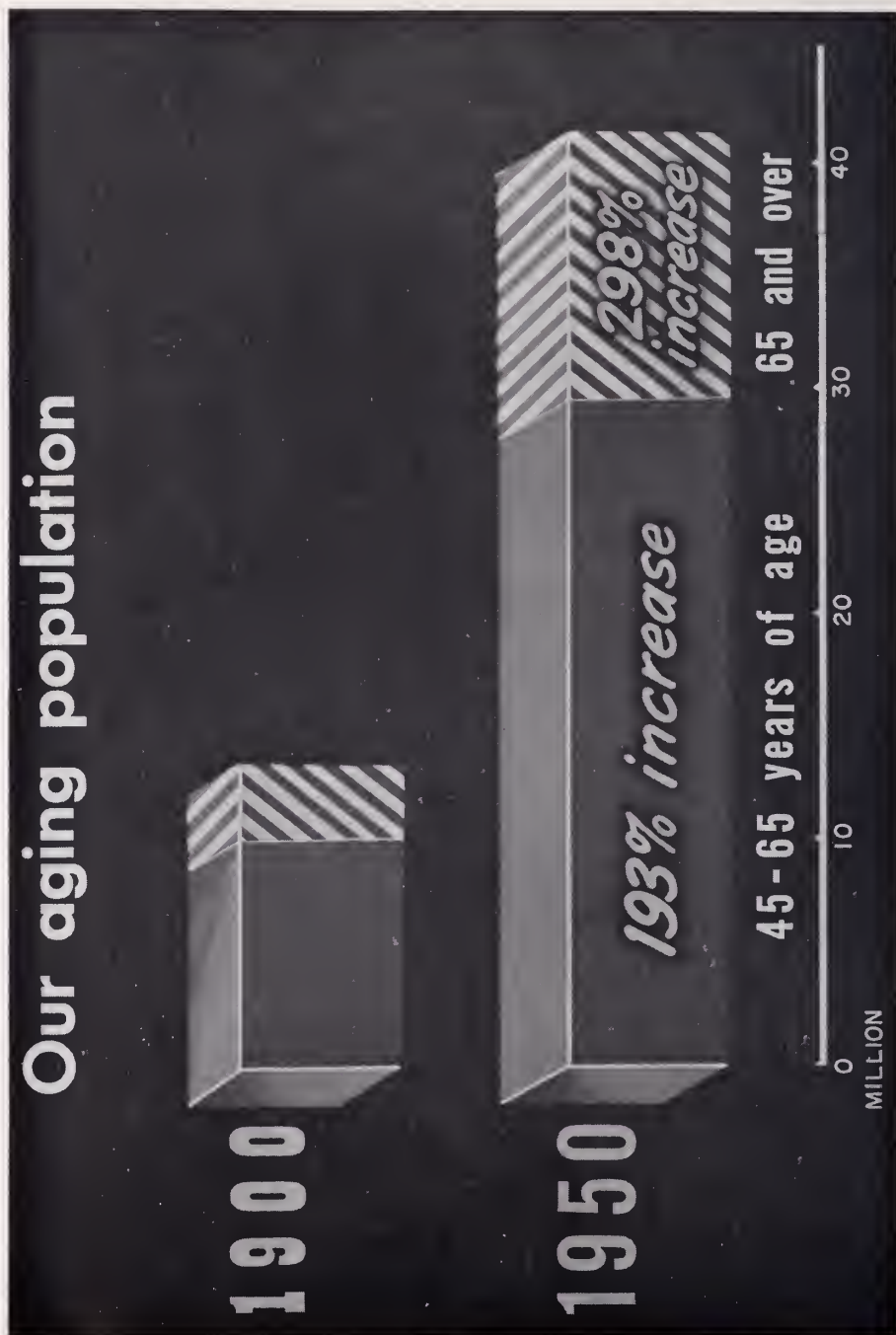


Fig. 3.

Major causes of death today

Disease	No. of deaths	% of total
Diseases of the heart	518,568	35.2
Cancer and other malignant neoplasms	206,325	14.4
Vascular lesions affecting central nervous system	149,953	10.3
Accidents	90,106	6.2
Diseases of early infancy	64,179	4.4
Pneumonia	40,038	2.6
Tuberculosis	39,100	2.6
General arteriosclerosis	30,426	2.3
Nephritis	25,935	1.7
Diabetes mellitus	25,089	1.6

60%

FIG. 4.

public administration; and life and health may be saved or lost, and they are actually saved or lost, as this authority is wisely or unwisely exercised." (5)

Public Health Organizations

A hundred years ago, no State had established a permanent board of health, and existing legislation defining the powers and duties of local health authorities was inadequate, confusing, and conflicting.

The proposals of Shattuck and his associates were not put into effect until 1869—nearly twenty years later—when Massachusetts became the first State to establish a permanent board of health and enact far-sighted legislation strengthening the organization and administration of municipal health work. In 1871, only three other States—Virginia, California, and Minnesota—had followed the lead of Massachusetts. Today, every State and territory has a well-organized health department (Figs. 5 and 6).

By 1873, only 32 of the major cities and towns in the United States had health departments (6). As urban areas developed from the last quarter of the century onward, the need for municipal health services increased and health departments in large cities multiplied rapidly. The concept of a well-organized city health department, supervised by a full-time medical officer of health, however, did not gain wide application until the 1920's. In that period, a survey of municipal health programs, conducted by the American Public Health Association and the United States Public Health Service, led to progressive improvement in administrative practices, and it stimulated the establishment and strengthening of municipal health departments.

The provision of local health services for rural areas began to claim attention prior to World War I, with the establishment in Yakima County, Washington, of the first full-time county health department. The development of full-time local health services is indicated on the map which shows the coverage for 1950.

Seventy-five percent of the American population now has some form of full-time local health service—city, county, or multi-county,—administered by state or local authorities. One of the handicaps to the extension of local health services has been the lack of adequate state legislation defining the powers of local authorities. Since 1940, however, legislation enacted in many states has gone far toward removing this handicap (Fig. 7).

In 1850, the only national agency concerned with the health of civilians was the United States Marine Hospital Service—predecessor of the U. S. Public Health Service. Its major function was the provision of medical and hospital care for sick and injured men of the American Merchant Marine. An Act of February 25, 1799, had provided that Federal officers were to cooperate with State and local authorities in the enforcement of quarantine laws and regulations. In the face of unusually severe epidemics, the Congress also from time to time passed special acts authorizing the Marine Hospital Service to take action in curbing the outbreak.

In 1870, the year after Massachusetts passed her historic health law, the Marine Hospital Service was first organized as a national agency with a mobile corps of physicians available for duty anywhere and at any time that the na-

Historical development of state health organization



Date of creation of each state board of health

FIG. 5.

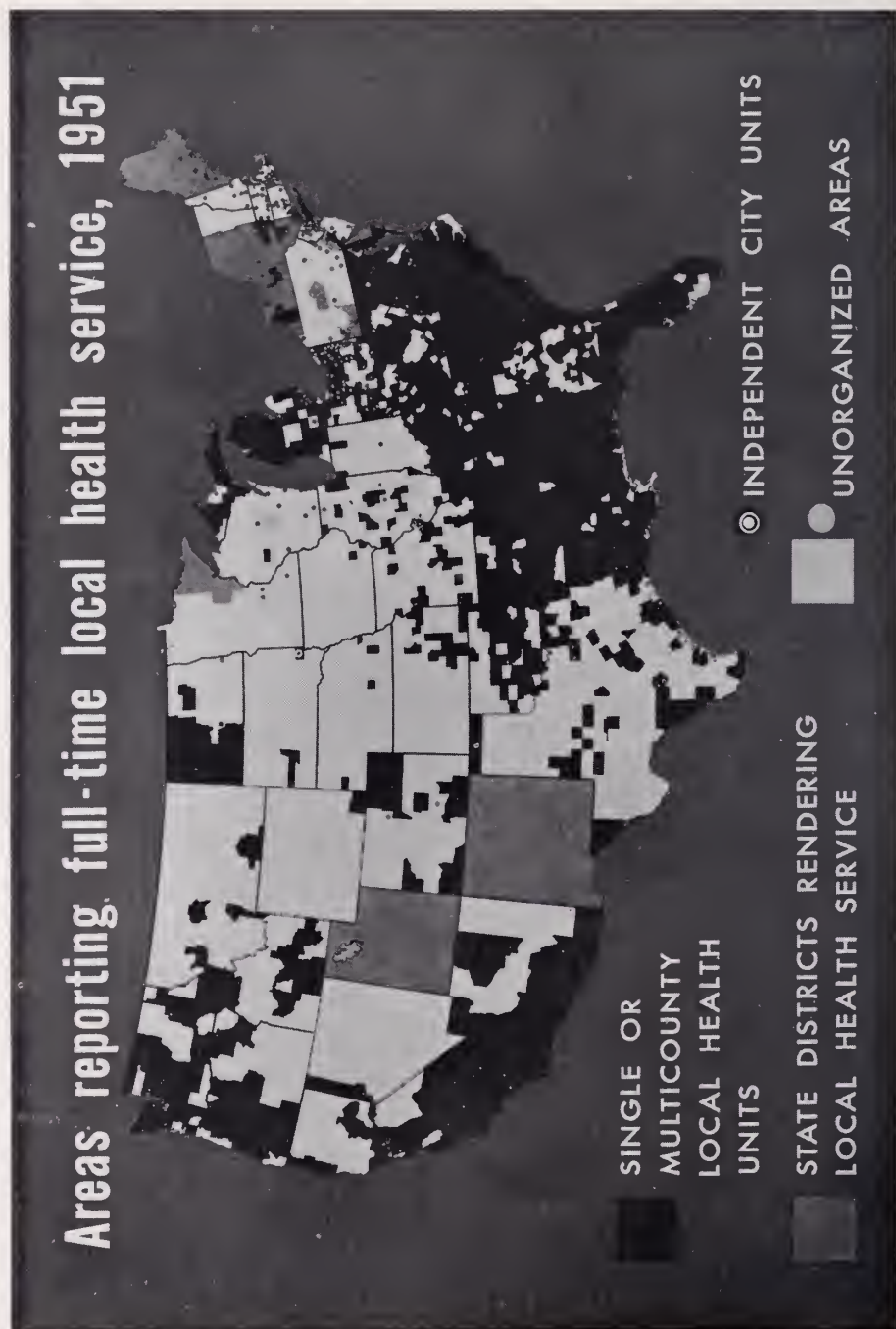


Fig. 6.

Legislation authorizing PHS programs

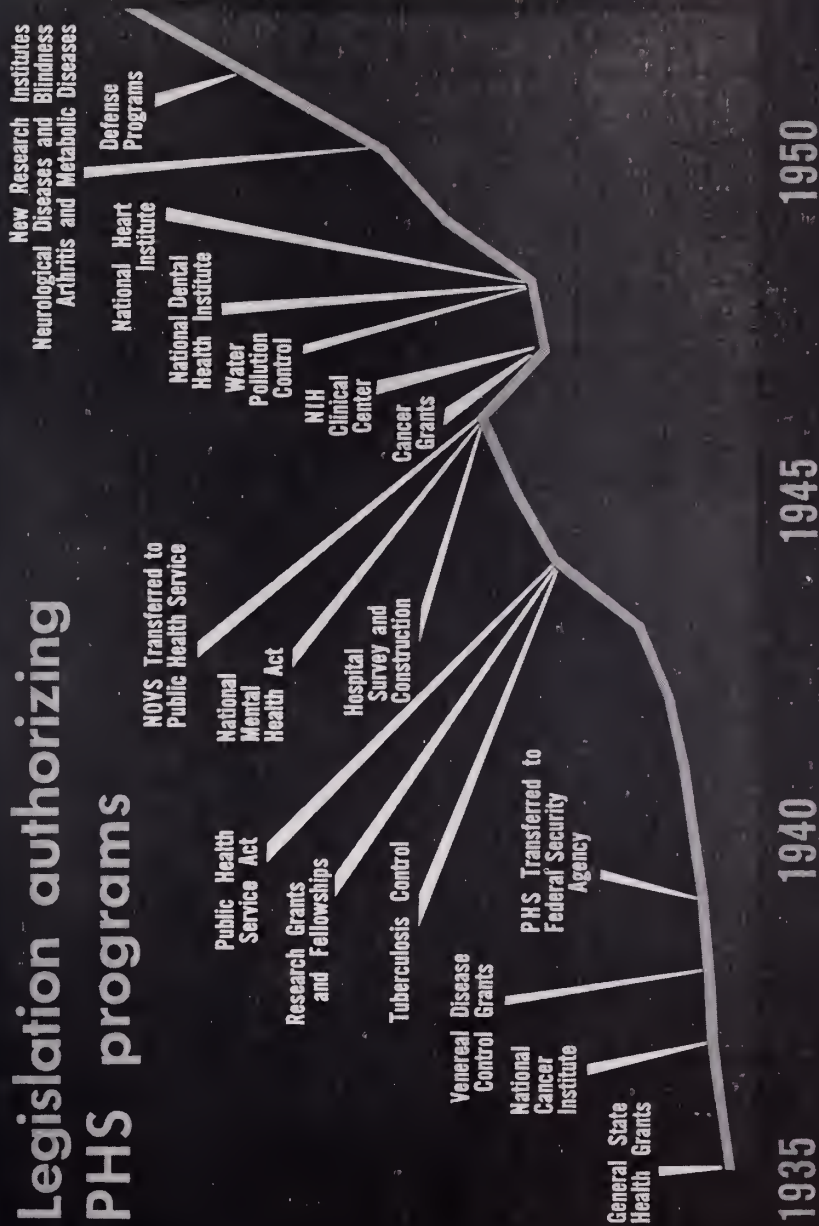


FIG. 7.

tional safety demanded their services. Not until 1893, however, did Congress pass legislation providing specifically for the control of the interstate spread of disease through cooperative activities between the states and the Marine Hospital Service. This principle of cooperation has been the key of all subsequent Congressional legislation providing for federal assistance to the States in health matters.

The United States Public Health Service and the United States Children's Bureau—the latter established in 1915—have been charged by Congress with the administration of the majority of the federal grants-in-aid programs for public health purposes. The initiation of these cooperative programs is illustrated in this chart (Fig. 7). The functions of the Public Health Service also have been expanded by Congress in the same period to include provision of research grants and fellowships to the Nation's medical scientists and research institutions.

The growth of public health organizations has been impressive. These charts, however, have not included the full development of health services in the structure of federal, state, and local governments. Nor have they covered the parallel development of voluntary services and programs. The record I have presented here is only a partial one.

The work of the Food and Drug Administration, the Office of Vocational Rehabilitation, of several agencies of the Departments of Agriculture and Labor, and of their state and local counterparts, come readily to mind as important elements in the total services related to the Nation's health.

The voluntary hospitals and health agencies constitute a major and vital part of the Nation's total health resources. The wonderful hospital whose centennial we celebrate today sprang from a common religious impulse: individual and social concern for the poor, the weak, and the fatherless. A hundred years ago, the vitality of that impulse sought outlet primarily through the establishment of institutions. Hospitals under religious auspices today account for nearly a third of the total annual admissions to non-federal general and allied special hospitals.

The Nation's voluntary secular health agencies—supported by public subscription—have increased in number and strength since the movement was launched nearly fifty years ago. Today, they are strong partners of the official agencies at every level of society—local, state, national, and international. They have spearheaded and accompanied public health progress every step of the way.

In the same period that the modern public health movement came to life in Europe and the United States, faint stirrings of international cooperation began. The first international health conference was held in Paris in 1815, chiefly to discuss the problems of the spread of epidemics related to the annual pilgrimage to Mecca (Fig. 8).

The situation today is a marked contrast with that of a century ago. International cooperation in the interest of health has evolved from those early explorations into a strong World Health Organization, working closely with 72 member states, other specialized agencies of the United Nations, and with more than 20 voluntary international societies (Fig. 9).

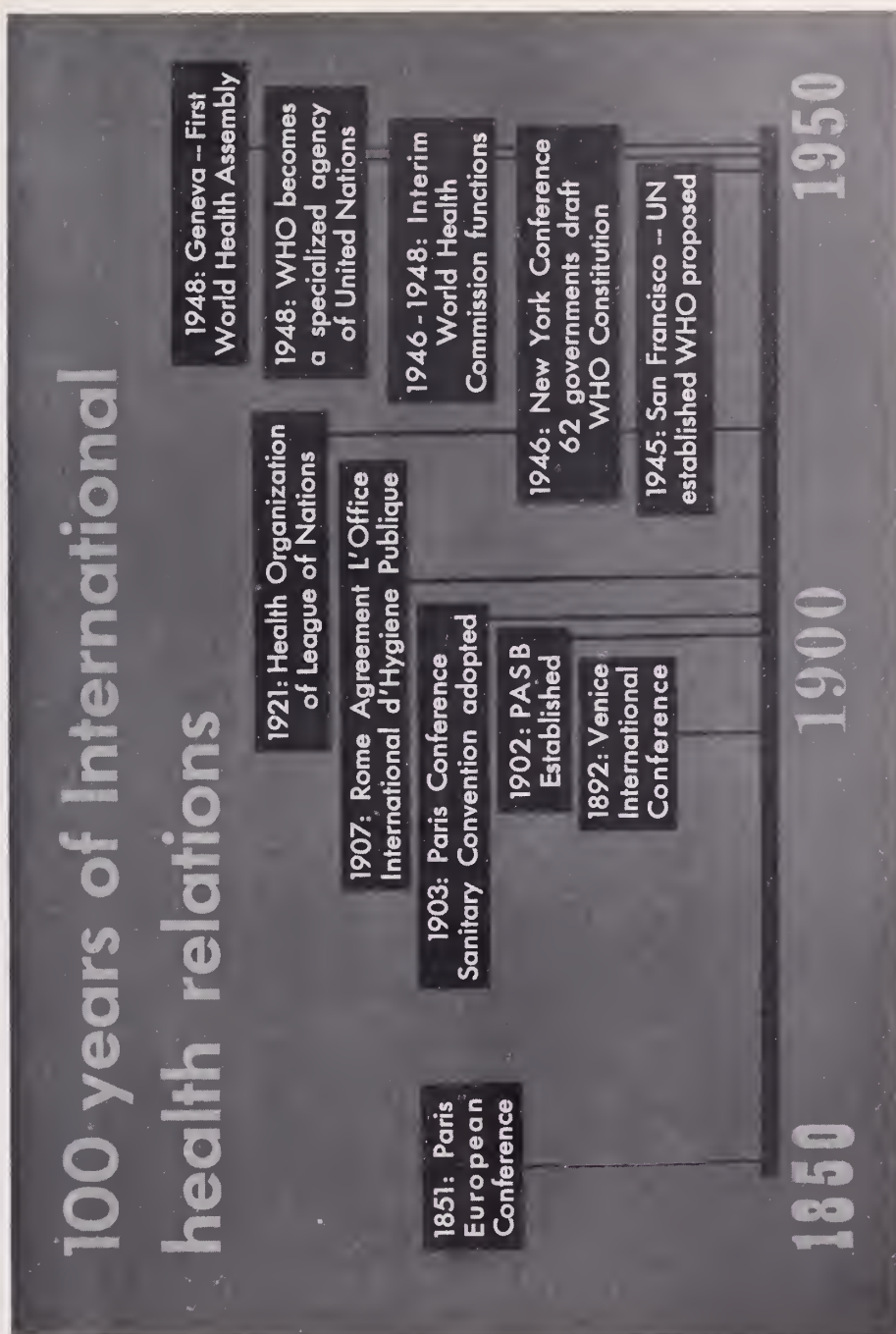


FIG. 8. Chart showing evolution of the World Health Organization.



FIG. 9.

The work of the WHO through the World Health Assembly, the Executive Board, the Secretariat, and six Regional Offices touches all of us in one way or another. Consider, for example, that in 1851, the Paris conference ended without accomplishing any agreements to prevent the spread of epidemics related to the pilgrimages. A century later we could rejoice in a magnificent achievement by national and international health agencies during the pilgrimage of 1951. Not a single case of pestilent disease in the movement of more than two million persons; not a single death from disease acquired during the pilgrimage was reported!

Public Health Personnel

Public health has always required a variety of professional skills, specifically adapted to the solution of broad socio-health problems. As Dr. William P. Shepard has said, "We stem from several professions: medicine, dentistry, engineering, nursing, education, social work, and others. That we should all have become further professionalized under the ideology of public health is a phenomenon worthy of note and of great significance to our future." (7)

Aside from quarantine, the foremost development in the first twenty-five years of public health,—and indeed, the only practical means available for the prevention of disease—were accurate statistical measurement of health problems, sound legislation, city planning, and sanitation of the environment. Thus, from the outset, we find statisticians, actuaries, lawyers, civil engineers and chemists in the forefront of the public health movement along with physicians. With the advent of bacteriology, a new battalion entered the ranks—scientific investigators in many disciplines, medical and non-medical.

From 1900 onwards, the emphasis in public health shifted rapidly from engineering methods and law-enforcement to medical methods and health education of the public. With this shift, the role of the physician increased in scope and importance—a logical result of the rapid development of biologic agents for the prevention and cure of communicable diseases; laboratory diagnostic techniques; pediatrics and prenatal care; modern sanatoria for the tuberculous; chemotherapy for venereal infections, and so on.

Early in the present century, under the leadership of medical administrators, public health turned to the nursing profession for its missionaries to the American home. The public health nurse, like the medical social worker, is one of America's original contributors to the evolving fields of public health and hospital administration.

Within the past twenty-five years, the science and art of public health have been enriched by the contributions of dentistry, veterinary science, education, dietetics, psychiatry, and many other professions. In 1932, the American Public Health Association set up a Committee on Professional Education. Fifteen years later, the Committee's very able chairman, Dr. William Shepard, could report outstanding accomplishments (8).

Educational qualifications had been specified for upwards of 20 professional specialties in the field of public health. These included public health administra-

tion, several medical specialties, and qualifications for such other specialists as the laboratory director, public health statistician, engineer, nurse, dentist, and educator.

Another major accomplishment of the APHA has been the accreditation of schools of public health. The accreditation study was conducted by Prof. C.-E. A. Winslow of Yale, and was financed by the Commonwealth Fund and the Public Health Service. Today 11 universities in North America are accredited to give graduate degrees in public health, and they have an average enrollment of about 700 students, of whom about 425 receive advanced degrees (9).

Commenting on this program, Dr. Shepard has said, "To my knowledge this is the first occasion in modern times that a learned profession has kept its educational house in order as it developed. . . . We have been spared the developmental blight of having ranks flooded with pseudo-trained people. We have jumped directly from apprentice training to well organized schools. We know what constitutes a good school, approximately how many graduates we need, and approximately the number of schools needed. Better people will do better work for public health in the future. Public health will flourish unfettered by the handicap of many incompetents in the professional family." (10)

That family has grown steadily in the past fifteen years, but is still far below needs. The most reliable annual estimates show 46,000 full-time employees in State and local official health agencies in 1947, and about 51,400 in 1951 (11). Comparable data are not available for voluntary agencies and industrial health services.

Public Health Facilities

Facilities under the operation of health agencies are another index of the growth of public health. Were the data and the time available, I am sure that the evolution from "pest-house" or "fever hospital," to the all-purpose, combined community hospital and public health center would be a fascinating story. So too, would be the liberation of many public health laboratories from smelly little back-rooms in the city hall or courthouse to the fine modern buildings of today.

To sharpen the focus, we can report that in 1946 there were approximately 1,000 separate public health centers in the country, chiefly in large metropolitan centers. With the assistance of the National Hospital Construction Program, State and local health departments have constructed an additional 300 centers in separate buildings. Many community hospitals constructed in the same period have included quarters for the local health service either under the same roof or on the hospital grounds. Many additional ones have been constructed without Federal aid.

PUBLIC HEALTH PRACTICE

Our physical and social environment in the United States has changed very rapidly in the past century. Thus we are challenged by a highly industrialized environment, by shifts in the age distribution of the population, and by the very successes of our efforts to prolong life.

On the other hand, in large areas of the world many centuries have passed with little change in the environment. Our brothers in these areas are challenged by health problems that closely resemble ours of a century ago: high death-rates, especially in the first years of life; absence of sanitary facilities and personal hygiene; and high prevalence of communicable diseases—such as malaria, intestinal infections, and even smallpox—which are no longer serious threats to us.

Specific health activities will necessarily differ from one country to another, and within any given area. This does not mean, however, that public health practice is not pertinent in some fashion to all times and all places. For it is the peculiar genius of public health to have developed a science and art capable of adaption to the physical and social demands of any community anywhere in the world. Let us consider some of the major areas of public health practice.

Biostatistics and Epidemiology

Public health in the United States sprang directly from the application of statistical method and the study of epidemics. If anyone doubts this, let him give himself the pleasure of reading Stephen Smith's report on New York in 1865. So closely related were these two methods that it is hard to say which emerged first as a field for systematized research—biostatistics or epidemiology. We can say, however, that these two are unique contributions of public health to medical science.

Statistical investigations are our best friend and severest critic: Our friend, because they delineate objectively problems that we had not recognized; our critic, because as Shattuck wrote, "they are the judgments of the time upon itself; and, untinged as they are by party spirit and unswayed by personal considerations, those judgments are as true and faithful as those of future times can be." (12)

Shattuck's interest in statistics was an important influence on the ultimate development of a system of national vital statistics in the United States. Massachusetts had had local mortality reports from Colonial times, but Shattuck established a state system and greatly improved and extended the collection and analysis of health data in that state. The young United States Government had early taken on the function of a decennial census, but we have had a slow development of collection of national vital statistics. A National Office of Vital Statistics was first established in the U. S. Bureau of the Census in 1900 to encourage the states to develop a uniform system of registration and tabulation of vital data. The Death Registration Area at that time included only ten states; after 1900, the area grew and a Birth Registration Area was established in 1915. Since 1933 our national collection of vital statistics has covered all states and territories.

The concept of longitudinal studies of community sickness and mortality experience was originated more than thirty years ago by the late Edgar Sydenstricker of the Public Health Service. In 1921, we began our studies in Hagerstown, Maryland, a small urban community with a social structure considered

fairly typical of American life. Hagerstown has a relatively stable population—a decided advantage for long-term studies. The medical and dental professions, the health authorities, schools, and industrial and civic groups of Hagerstown have been our constant collaborators. We now have data on the sickness and mortality experience of several generations. More than 100 scientific papers have been contributed in the Hagerstown Studies, throwing light on the relation of health defects in childhood to adult health; the effects of socio-economic changes upon family health; the development of chronic diseases in the family from generation to generation; and many other significant factors.

Sickness surveys conducted in the past twenty years by various organizations, including the National Health Survey conducted by the Public Health Service in 1935–36, have given us a clearer understanding of the variations in the level of health in our changing society. Data from the National Health Survey provide the basis for the most accurate estimates available of the current prevalence of chronic diseases and impairments. We are, however, seeking new techniques for measuring current prevalence.

These statistical studies have incorporated many of the socio-economic factors which played such a prominent role in Smith's house-to-house canvass nearly a century ago. As those early surveys were springboards for the development of the epidemiology of communicable diseases, the latter-day studies have stimulated the epidemiologic approach to chronic disease, impairments, and accidents.

Epidemiology has been defined as the science of "the relationships of the various factors and conditions which determine the frequencies and distribution of an infectious process, a disease, or a physiological state in a human community." (14) Such a concept accounts for the wide variety of epidemiologic studies that have led to the solution of critical public health problems other than epidemics.

In many instances, epidemiologic study has led to the elucidation of the specific etiology of a disease. The work of Goldberger in pellagra is a classic example of this result. Often, however, epidemiology has led to methods of control prior to discovery of a specific cause. The fluoridation of public water supplies as a means of controlling dental caries, for example, is based upon classic epidemiologic studies. This is a case where a control method has preceded elucidation of the etiology of dental caries and the mode of action of fluorine in preventing caries. On the other hand, full understanding of the epidemiology of a disease often has had to await answers to puzzling questions from research in the basic sciences.

The epidemiologic approach has always required study of large segments of the whole community—the well, the sick, the total physical and social environment. Thus epidemiology and public health practice have much to offer medicine. Young physicians entering the Public Health Service often tell us that assignment to an epidemiologic study has been a revelation to them. For the first time, they tell us, they have had a chance to see and examine a great many healthy people; for the first time they have gone into the community to trace factors contributory to disease; and for the first time they have worked on a full public health team.

Communicable Disease Control

Despite the victorious attack upon the parasitic diseases—as Pasteur termed them—communicable disease control is by no means “a burnt-over field” in public health today. In international health work, there is the formidable task of adapting well-established methods and modern agents to the physical and social environments of tropical, semi-tropical, and under-developed countries. In our own country, there is the continuing quest for more effective methods and agents, and for control of infections not susceptible to existing methods.

Intensive experimental and epidemiologic research within the past quarter century has greatly expanded our knowledge of the smaller micro-organisms. In the past decade, in fact, we have witnessed the identification of entirely new disease entities—such as rickettsialpox; the discovery of new reservoirs of previously known infections, as in the case of Q fever; and the apparent demonstration of distinct agents associated with some of the diseases in that vast range of ill-defined “minor respiratory illnesses.”

A major contribution in the last-named field has been the recent recognition of the Cocksackie viruses, an entirely new group of viruses, and the identification in this group of 15 immunologically distinct disease agents which were completely unknown three or four years ago (15). Studies by the Microbiological Institute of the Public Health Service on two of the Cocksackie diseases—herpangina and epidemic pleurodynia—have contributed certain facts from which new research in the general field of virology is being developed. The importance of this work is enhanced by biological similarities of the Cocksackie viruses to the poliomyelitis viruses.

Progress toward the control of some of the older virus infections also can be reported. The World Influenza Center of the World Health Organization, with its international network of laboratory “listening posts” now broadcasts prompt, reliable information about the movement of specific strains of influenza virus. The United States Influenza Study Program, with headquarters at the National Institutes of Health of the Public Health Service, participates in the world program. In 1951, a cooperative demonstration with certain pharmaceutical manufacturers, showed that a vaccine against the major strains of virus involved in an epidemic can be produced rapidly and on short notice. This leads us to believe that if confronted with a nation-wide epidemic or pandemic, the United States could produce large enough quantities of vaccine in time to restrict the rapid spread of especially virulent strains of influenza virus.

With the past two years, the Public Health Service has established a Sectional Research Program in Microbiology and an Epidemic Intelligence Service as additional efforts for more effective procedures in the control of infectious diseases, including epidemiologic and laboratory investigation, immunization, diagnosis and therapy. No less than 98 laboratories, organized in 11 sectional groups, have voluntarily joined the Sectional Research Program, and the Epidemic Intelligence Service is available to state and local health departments. These new services are of importance to the Nation at any time, but would be indispensable in the event of emergencies or of enemy action.

Encouraging reports of experimentally effective preventive vaccines for poliomyelitis have come from two independent investigators in the past few months. The work of Herald Cox and his associates and of Howe and his co-workers justifies the hope that the long-awaited, inexpensive agent for control of this virus infection may be in sight. Hammon and others also have reported the efficacy of gamma globulin in reducing the incidence of paralytic poliomyelitis.

Public health pioneers frequently prescribed "eternal vigilance" as a responsibility of health agencies in the control of communicable diseases. No activity more forcibly illustrates this requirement than does malaria control. Intensive application of DDT and other new insecticides in malarious areas of the United States began in 1945. During the past six months, after nearly five years of virtual freedom from malaria acquired in this country, 16 cases among civilians have been proved indigenous. Although the figure is small in comparison with the total of about 8,000 relapsed cases reported since January 1, 1952, the indigenous cases are of great public health significance because they show that malaria infection is again being transmitted within our borders. Control of the mosquito vector remains an effective and inexpensive preventive measure, but a better answer to re-introduction of malaria would be more effective preventive agents for American troops and civilians in malarious areas overseas. A new drug, pyrimethamine, offers great promise as a preventive chemotherapeutic agent and the Public Health Service is conducting clinical trials of this drug in cooperation with the armed forces.

There are many other unsolved problems in communicable disease control, but I shall pass now to consideration of another major area in public health—namely, environmental health.

Environmental Health

The brilliant successes of Sedgwick, Frost, and many other pioneers in environmental health gave society virtual control of hazards which once spread intestinal infections and insect-borne diseases like wild-fire. The Herculean task of creating safe water, milk, and food supplies for a large proportion of an increasing population has been accomplished. Many of the traditional sanitary practices of public health are now readily accepted and kept in practice. We are, however, living in an environment quite different from that of fifty years ago—or, for that matter, even ten years ago.

Public health can no more ignore this new environment as a possible source of ill health than our professional ancestors could ignore the environment of their times as a source of devastating epidemics. Moreover, we now think of the environment in a wider dimension—to include social and psychological factors along with the physical.

Stephen Smith described in graphic detail the housing conditions in which he found the foci of infectious diseases. Seventy-five years later, Winslow and his associates began the significant studies sponsored by the American Public Health Association on the hygiene of housing. From these long-term studies, public health has evolved a basic technique for the measurement of the hygienic quality of housing. And today—public health teams are studying the effect of housing

on mental ill health, fatal or disabling accidents, and such chronic ailments as heart disease, arthritis and rheumatism.

Nowadays, none of us can escape the influence of chemicals on our daily living. For the most part, that influence has been beneficial to a high degree. But in the field of public health, we are beginning to see clouds upon the horizon—literally. The problem of air pollution, for example, is no longer confined to our work places or to our largest industrial centers, but is a potential threat to health in semi-rural and even some rural communities. In most of our cities and metropolitan areas, smoke and fumes of unknown toxicity are produced by factories, large business, residential, and institutional buildings, motor vehicles, and railroads.

Public health knowledge of chemical and radiological hazards began with the study and control of occupational diseases. Today, the number of known substances, compounds, and processes used in industry runs into the thousands and is being increased day by day. Study of occupational disease and its environmental sources, therefore, remains an extremely important field of public health, requiring cooperation between management, labor, private and governmental agencies.

To what extent the industrial uses of chemicals and radiological substances affect the health of the general population is not known with anything like the specificity of our knowledge of occupational hazards. The pollution of the Nation's waters by industrial wastes, for example, is one of the largest domestic problems facing this country. It involves our total economy—and is a present threat to industrial expansion, agriculture, recreation, fish and wildlife, and public health.

We are still far from understanding the new industrial pollutants, as well as from solving this growing problem. During the past four years, the Public Health Service has worked with state and interstate water authorities and industrial groups to stimulate research in this field. We are cooperating also with the Atomic Energy Commission in studies of the disposal of radioactive wastes. The current work, however, in both chemical and radiological pollution is only a small beginning of what is destined to become a large field of public health research and control.

The addition of chemicals to many processed foods and the development of new physical techniques for the preservation and transportation of foods also require study. For example, the Select Committee of the House of Representatives to Investigate the Use of Chemicals in Foods and Cosmetics—the Delaney Committee—recently reported (16) no less than 704 chemical substances now added to foods. In most instances, very small amounts are added; but it is clear from the Committee's report that more research is needed to determine the effects of many of these chemicals in foods on human health.

Chronic Disease Programs

The growth of voluntary and governmental programs concerned with specific diseases has been mentioned in preceding sections of this paper. The phenom-

enon, however, deserves thorough study by voluntary and official agencies, the professions, and the public at large, for the end is not yet in sight.

Whether the programs directed at specific diseases or groups of diseases can be—or how they may be—welded together into a logical, effective plan for raising the level of health in the population of the United States is the foremost public health challenge in our changing society.

The major expansions of both voluntary and governmental health programs in the past decade have been in the so-called chronic diseases and permanent impairments. One can mention, for example, new or expanded programs on alcoholism, arthritis and rheumatism, blindness, cancer, cardiovascular diseases, cerebral palsy, deafness, diabetes, epilepsy, mental disease, multiple sclerosis, muscular dystrophy, other neurological diseases, and tuberculosis, among many others.

In 1934, Dr. William H. Welch described this phenomenon of our American public health movement with such wisdom that I can do no better than use his words: "These newer directions of public and individual health . . . have been re-enforced and greatly expanded by similar popular movements organized to promote maternity, infant and child hygiene, social hygiene, mental hygiene, the control of cancer, the prevention and relief of heart disease. . . . Among the great lessons taught by these recent health movements is the necessity for securing the cooperation of all the forces of society, both governmental and voluntary, in support of efforts of health departments and the medical profession to prevent disease and improve health. . . . The most important lesson of all is that success is dependent upon accurate knowledge . . . and that the hope of the future lies in increase of useful knowledge by the methods of experimental science." (17)

These are the goals of voluntary and governmental health programs concerned with specific diseases, and we are moving toward them. The rate of progress varies from one program to another, but it can be said that up to now we have learned more about how to weld together the expanded research efforts on chronic disease than about the development of preventive and early detection programs to which all the forces of society can subscribe.

In 1950, 1,193 local health organizations reported on the clinical services operated in their areas by official and voluntary agencies. Four in every five health departments reported tuberculosis clinics; three-fourths, venereal disease and well-child clinics; three-fifths, maternity clinics and general clinics for crippled children. Nearly 40 percent reported cancer diagnostic and treatment centers and well over one-fourth, mental hygiene and pediatric clinics. Some of the newer special programs,—such as cardiovascular disease, diabetes, cerebral palsy, rheumatic fever, epilepsy, and otological clinics—were reported by from 10 to 20 percent of the health departments (18). These programs have been developed in cooperation with private practicing physicians of the areas and in most instances are staffed by them. The basic public health principles of prevention of disease and promotion of health underlie each of these programs.

There is an acute, practical need for extension of preventive programs in

chronic disease. The volume of chronic disease and impairment is increasing, and with it the demands for facilities and personnel to care for the seriously ill and injured. The costs of care have also increased step by step with advances in medical technology. The economic burden upon individuals, families, and the Nation as a whole is already heavy. Until all of us pick up the front end of the burden—the preventive aspect—the Nation will never be able to meet adequately the needs for medical and hospital care. Moreover, until more attention is paid to prevention, more and more people will reach what one of our British colleagues has called a state of “medicated survival.” The prevention of chronic disease, from this viewpoint, should be a joint responsibility of all the professions, all the health and welfare agencies, all the hospitals, and all of the people.

Promotion of Personal Health

Public health has yet another enduring goal: health as a positive factor throughout the life-experience of an individual. Perhaps one reason that society has not responded to the challenge of health so enthusiastically as it has to the challenge of sickness is because we in the health professions have been too preoccupied with disease.

The concept of “health” itself is not easy to translate into a goal which one may work toward. Even the definition adopted in 1946 by the World Health Organization of health as “a complete state of physical, mental, and social well-being, and not the mere absence of disease or infirmity”, is difficult for the average individual to understand and visualize as an attainable goal. On the other hand, a magic cure for cancer or muscular dystrophy, for example, is easily visualized as a goal, for there have been so many “magic cures” for other diseases. As long as the professions are too preoccupied with combatting disease, we cannot expect the public to accept new concepts and adopt new approaches to their health problems.

Thus, the concept of personal health has had little realization except in the fields of child welfare and pediatrics. Medicine, public health, and social service have found ways to make that complete state of physical, mental, and social well-being in the child an attainable goal in the eyes of parents, teachers, and other responsible adults. Few responsible citizens today, for example, find it difficult to visualize a radiantly healthy child. Health even for the physically or mentally handicapped child—within his limitations—is readily conceived. To the goal of child health, therefore, the public has responded with enthusiasm and enduring support. Up to now, however, our attitudes toward the health of the general population are more influenced by our consideration for the patient than by the concept of healthy men and women, healthy families, and healthy communities. As the proportion of middle-aged and elderly persons continues to increase, the health of adults becomes an increasing challenge both to public health practice and to medicine. We need not only a firmer scientific foundation for a practical hygiene of the aging, but also more effective methods for motivating adults in all age groups to adopt practices that will help protect and promote personal health.

PUBLIC HEALTH RELATIONSHIPS

Health is recognized as an inseparable element in social progress at all levels: local, state, national, and international. Public health does not and cannot function in isolation from the political, economic, educational, and cultural forces in society. Nor can industry, commerce, agriculture, education, or government function in isolation from public health.

These relationships have grown up, rather like Topsy, in our country, so that their importance and meaning do not impress us forcibly. Perhaps the world health movement in which the United States is so active gives us the clearest understanding of what these relationships mean. The technical assistance programs operated by the United Nations and by the United States Government, are moving rapidly toward a rational coordination of activities aimed to improve the economic, health, agricultural, and educational status of underdeveloped areas. The problem of coordination, however, is not easy to solve.

In our own country, we have many comparable problems of organization. It is not yet clear, for example, how public health can (or should) function in other important programs which have significant health components. Among these, one thinks especially of the health aspects of public assistance; of public medical services; vocational rehabilitation; public housing; civil defense; and voluntary hospital and health insurance plans.

There is ample room for research and experimentation in this relatively unexplored area. Only two or three states have integrated their public health and public medical services, for example; and the current operations are primarily on an empirical basis. There are very few studies and demonstrations in progress on the utilization of our health resources and these are focused each on a single or a few facets of what are in actual fact, much broader problems. There are studies on the development and utilization of nursing services, for example; on the coordination of hospital services in a few areas; and several in the general area of what we call "medical economics." So far as I know, however, there are no examples of broadly representative social research, involving all of the major sciences involved in the solution of a community's total health problems.

We need guides to more efficient and economical administration of our health and medical services which such studies might provide. We need also guides to a more profound problem: how can we bring about better cooperation among public health and other official agencies, private medicine, and voluntary hospitals. Without such cooperation on both sides of the street, the people of this country may have to wait several generations for any substantial progress in the prevention of disease and the promotion of health in the great impact area—our aging population.

The challenge implied in my observations is not to public health alone or to medicine alone, but to all other social institutions and to society itself. As we have listened to the stimulating discussions from this platform, I am sure that all of us have been challenged—by the awesome sweep of history in the life-time of this hospital, by the magnificent achievements and stirring hopes of medicine.

I am just as sure that our response to that challenge will be a resounding affirmative to Stephen Smith's demand for better health and longer life in our changing society.

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MEDICINE AND SOCIETY: THE ROLE OF PSYCHIATRY

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It is indeed a high honor to have been asked to participate in this Symposium on Medicine and Society to commemorate the 100th anniversary of the incorporation of The Mount Sinai Hospital in New York. Any hospital that has served the public for 100 years should certainly rate a special celebration. Mt. Sinai, however, is a very special hospital that has given far more to the world than merely the service to the thousands of patients who have come and gone in these 100 years. From its laboratories and its bedsides have come a long list of distinguished contributions to medical science that have brought to this hospital a reputation throughout the world.

There is a special and personal satisfaction for me to participate in this Centennial. Under the guidance and leadership of my long time friend and colleague and medical officer in arms, Dr. M. Ralph Kaufman, Mt. Sinai has developed a psychiatric division in this general hospital that is outstanding. It has few, if any equals in the effectiveness of its integration throughout the hospital, its diagnostic and treatment program both in the in-patient and the out-patient services and the unusually high caliber of its residency training program. In my critical and objective judgment, I can report to you, the friends of this hospital, and to its Trustees, that Mt. Sinai is again making history.

On this occasion, it is a real privilege to present my interpretation of the role of psychiatry in medicine and its impact on society today. Psychiatry is one of the youngest of the specialties of medicine. One might question whether or not we have sufficient perspective to evaluate the impact that it has had and is having. One might be skeptical, justifiably, as to whether or not a psychiatrist, especially one who holds strong convictions about the worthwhileness of his specialty and is enthusiastic over the possibilities of its future should make such an evaluation. However, I hope that you will accept my remarks with the recognition of the limitation common to all of us: one's judgments are based on his own experiences and knowledge. This is the more true when one is discussing so vast a field as psychiatry has become. It is a rapidly growing science, with too few tenets in which there is firm agreement and with an unusual number of ramifications and specialized interests.

THE EVOLUTION OF PSYCHIATRY

One of the working principles in the practice of psychiatry, if not of all medicine, is the necessity to know the past in order to interpret the present. The best way to understand the current status of psychiatry is to have some understanding of the past development. For this reason, a brief sketch in the grossest outline of the evolution of this medical specialty should provide the framework for a better grasp of the role of psychiatry in medicine and society today.

For the sake of brevity, I shall ignore the very high level of achievement in

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medicine in the golden age of Greece. During the 1,000 years that followed, generally known as the dark ages, little or no progress was made in any field of science including medicine, and in fact, many previous gains were lost. It was an age of devastating epidemics of cholera, plague, leprosy and scurvy. Religious movements were rampant and included such freakish performances as the children's crusades, in which young children marched thousands of miles. During holy wars and crusades to the holy land, thousands of men lost their lives searching for the Holy Grail. There were nation-wide epidemics of flagellation, chorea and tarantula dances, all in the name of religious zeal.

During this time, man's attitude towards mental illness—if such could be distinguished—was a mixture of mysticism and religiosity. The body was considered of no importance in comparison with the spirit and the soul. Judgment of behavior was grossly distorted. In keeping with the misconceptions of the period, man was thought to be the prey of demons and his soul the battleground of the struggle between the devil and the Lord for its possession. The usual explanation of bizarre behavior was that the individual had become possessed by an animal or was a werewolf. Mystical figures and forces known as incubi and vampires, devils and witches were strongly believed to exist.

And then in the 16th and 17th centuries, sciences began to develop and with them the science of medicine. Because medical progress was almost entirely physical in nature, the early explanations of behavior, particularly mental illness, were mechanistic. The new and helpful discoveries in anatomy, physiology, infectious etiology, physical treatment, have remained the chief basis of orientation and approach to all medical problems. This "organic" approach has applied also to psychiatry until quite recently. The more intangible factors of feeling, thinking, emotion and behavior were largely ignored.

Through this era, only those individuals who were severely mentally disturbed—we cannot call them patients—received attention. They were segregated from the community and given over to the care of attendants, who played the role of prison keepers while they provided their charges with the poorest of food, straw beds, and vermin infested quarters. Those unfortunates were usually kept in chains in unlighted, unsanitary cells and were rarely given any medical treatment. In England, "mild mental patients continued to remain at home or to wander at large or—if without family support—were taken in by the alms houses. The violent were flogged, placed in stocks, locked up at home, or deposited in the local jail. . . . American villages were usually too small to provide alms houses or even jails; but it was assumed that local authorities were responsible for poor relief, including that of the 'insane.' The violent were confined at home, not only for protection but also because mental illness was keenly felt as a family disgrace. Poor relief was involved when a family felt unable to care for the sick individual, and then small funds were begrudgingly extended. Thus, in 1699, the town of Braintree, Mass., ordered the Selectman 'to treat with Josiah Owen about Ebenezer Owen's distracted daughter and given him 20 pounds money provided he gives bond under his hand to clear the town forever of said girle.' " (1)

The treatment of mental illness was really included as a part of rational therapeutic medicine only 160 years ago when, in 1792, a courageous French physician, Pinel, at the Bicetre in Paris took a group of psychotic individuals out of their chains, dungeons and unsanitary rooms and began to treat them as patients. Against the greatest of opposition, he brought about this reform to begin the so-called "open door" policy in the treatment of hospitalized mental patients.

One hundred years ago—when Mt. Sinai Hospital was incorporated—psychiatry, such as it was, was still trying to explain the origin of mental illness largely on the Greek theories of humeral pathology or that the "proximal cause" of such illnesses was some sort of irritation in focal areas of the brain. Treatment still consisted of bleeding and purging because of the beliefs that mental illness was due to "excessive action" within the patient's physical system, particularly as congestion of the blood vessels of the brain, and, by such therapeutic methods this was relieved.

In the most progressive of the 23 state mental institutions that existed at that time—the locale of essentially the sum total of the practice of psychiatry in America in 1852—the most idealistic form of therapeutic help in "insanity" was called "moral treatment." This was defined by Amariah Brigham, the superintendent of the Utica State Hospital in New York, in 1847, as follows: "The removal of the insane from home and former associates, with respectful and kind treatment under all circumstances, and in most cases manual labor, attendance on religious worship on Sunday, the establishment of regular habits and of self-control, and the diversion of mind from morbid trains of thought." (2) Another indication of the status of psychiatry as late as 1850, is the fact that the psychiatric nosologies based on symptom descriptions listed as many as 300 supposed mental diseases (3).

Psychiatry as we conceive of it today, began only 60 years ago with Sigmund Freud, when in 1890, he forsook neurology and devoted the remainder of his life, until 1939, to developing the most illuminating of all psychological and psychiatric contributions—psychoanalysis. Oberndorf (4) divided Freud's work into three general periods: the period of theory development from 1890 to 1905; the period of clinical application from 1905 to 1920; and the period of philosophical reflections from 1920 to 1939. Freud's formulations of the structure of the personality, infantile development, methods of investigating and treating personality disorders, the elucidation of the unconscious, and many other observations, have given us the solid base for what currently is termed "dynamic psychiatry."

It was only a little over forty years ago that some leaders in American psychiatry first came forth with the full support of the psychogenesis of mental illness, going against the then existing trend that mental illness was due solely to abnormal bodily conditions, either in the brain or elsewhere. William A. White's "Outlines of Psychiatry" was first published in 1907. That same year August Hoch expressed his firm conviction regarding the psychological origin of paranoid states, supported in 1908 by a paper from Adolf Meyer emphasizing

the same principle, and, in 1909 by a paper on the analysis of a case of schizophrenia by A. A. Brill (5).

The next major stimulus to American psychiatry was World War I. Dr. Thomas Salmon, the director of psychiatry in the American Expeditionary Forces, is credited with having described the war as playing Prince Charming to the medical Cinderella, psychiatry. He did so because of the relatively obscure position psychiatry held prior to the war in contrast to the enormous demands that were made upon psychiatrists in World War I. The immediate results were numerous: the beginning of psychiatric social work, the first general utilization of the clinical psychologist in psychiatric practice, the application of psychiatric experience in industry, the first attempts to apply psychiatric skills in understanding delinquency and crime, and a real impetus towards the establishment of community mental hygiene clinics for adults and children. From a practical point of view, all of these developments represented new extensions and applications of psychiatry.

The result of the impact of World War II on the development of psychiatry has been phenomenal. At its beginning, so far as the military organization was concerned, the lessons of World War I seemed to have been forgotten. Then, the medical problems of personality disorders and mental illness were enormously increased as compared to World War I, in part because three times as many individuals were involved for a period of nearly four years, in contrast to the 18 months of World War I. There were nearly ten times as many admissions to the psychiatric services of army hospitals in World War II as occurred in World War I. Much was again expected of psychiatry, some of which it could deliver and some of which it could not, partly because the World War I experience had not been used.

Personality disorders, including mental illness, became the chief causes of the loss of manpower in World War II, more than from all other causes put together. This created major problems for command from the Chief of the General Staff down to the company commander.

Despite an attempted blackout of information about the seriousness of the psychiatric military problem, the press successfully carried the concern to the public. The psychiatric rejectees at the draft level and the many discharged psychiatric casualties brought the news home to the communities in a very personal way. The spotlight of public attention was focused on psychiatry. Ever since that time, those of us in this field have been working feverishly to try to deliver what was and is expected of us. Even in our most optimistic moments, we feel that we have been only partially successful.

So much for this back drop of the evolution of psychiatry. My assignment is to discuss the impact which it has had on the field of medicine; on society as a whole, and on the individual.

THE IMPACT OF PSYCHIATRY ON MEDICINE

The influence of psychiatry on the general practice of medicine was minimal until about 30 years ago when, in World War I, it became really important as a

medical specialty. There were many reasons for this state of affairs. Psychiatry began as an institutional practice, usually isolated and apart from the general hospitals and clinics. As a consequence, psychiatrists had minimal contact with other physicians. Until even 15 years ago, there were more psychiatrists whose total practice was limited to a psychiatric institution than the number who practiced outside of these institutions. Furthermore, until a comparatively recent date, the major concern of psychiatry was limited to those individuals who were so mentally ill as to require hospitalization, namely, those suffering with psychoses. This fact explains the erroneous impression still held by many individuals that psychiatry's chief work is the diagnosis and treatment of psychoses.

For so many years, the study of human behavior was not included in medical practice or education. Man was regarded as an anatomical-physiological-chemical unit and not as a social unit. Medicine concerned itself with the misbehavior of the stomach and the pancreas but not with the misbehavior of the total organism in relation to its environment. Probably the chief reason for the failure of psychiatry to become integrated into the general practice of medicine was the absent or deficient teaching of this specialty in the medical schools. The great majority of the practicing physicians of today who graduated from medical school more than 15 years ago were given a totally inadequate understanding of psychiatry during their medical education.

Over these last 30 years, the body of psychiatric knowledge has increased greatly, providing a more firm basis for the understanding of personality development and functioning, the forces of the unconscious and the conscience, the etiological factors and the treatment methods in many types of personality disorders. It has been the knowledge gained from psychoanalytic research and practice that has fructified and lifted psychiatry to a place where it can throw light on many types of illness, and thus be in a position to contribute to all medicine (6). Psychiatrists are increasingly able to provide helpful information regarding the emotional factors in illness to the internist, surgeon, and to the other medical specialists. With this increase in knowledge and the discovery of greatly improved treatment methods, there began a migration of psychiatrists from the strictly mental institutions into the general hospitals and clinics and into private practice. Today the majority of the psychiatrists practice outside of mental hospitals.

World War II brought about other changes in the relationship of psychiatry to medicine. War is a human activity in which there always has been and always will be a very high rate of emotional decompensation. Demands are made upon the individual personality which have no parallel in civilian life. Nearly one-third of the practicing physicians in the United States entered military service. There they were faced with a situation far different from that of a private or hospital practice in civilian life. They could not avoid seeing the extensiveness and the variety of personality deviations and maladjustments. Because the soldier or sailor who was unable to report for full duty was sent to the hospital, the doctor in military service encountered women and men who were incapacitated because of homesickness, countless varieties of physical complaints of emotional origin,

enuresis and alcoholism, maladjustment because of cultural or educational deficiencies. Medical training had not given most physicians any basis for understanding, let alone any scientific knowledge about how to deal with most of these types of human frailties. Some medical officers responded to the need for protecting their own lack of knowledge or their disinterest by name calling. The result was that many thousands of men and women were unfairly labeled as "psychos", weaklings, malingerers, eightballs, cowards and with other uncomplimentary terms. The use of such descriptions too often indicated a complete lack of an ability to evaluate and treat the problem. Fortunately, there were many other medical officers who responded with a healthy scientific interest and a desire to understand and find a treatment for these "new" (to them) kinds of incapacities.

The impact of psychiatry on medicine was greatly strengthened by the fact that every military hospital included a section of psychiatry, always an important and often a very large section. Thus psychiatry was not practiced in an isolated fashion as it had been so largely in civilian life. The psychiatrist and his colleagues in medicine ate together and worked together and lived together. The psychiatrist was convenient for consultation and in many of our larger hospitals the full time of one or two psychiatrists was constantly in demand for consultations on the medical, surgical, orthopedic and other wards. This was a new experience for most of the psychiatrists and their medical confreres.

Still one other phase of the military experience made great demands on psychiatrists and insofar as these demands could be met satisfactorily, gave stature to psychiatry. From the beginning of the war, psychiatrists were included in the selection and screening process in the induction centers. Regardless of one's opinion as to the effectiveness of that screening (most of us feel it was not well done), millions of American youth for the first time heard of psychiatry and had a personal contact with a psychiatrist.

With over a million admissions to the psychiatric services in army hospitals and many more than this number of contacts between psychiatrists and patients in the mental hygiene services and in the clearing stations at the front lines, many men really learned something about this specialty of medicine for the first time and from firsthand experience. Through them, millions of other Americans, the families and friends of these psychiatric patients, learned something about mental illness and psychiatry.

All of these historical events and factors, along with the greatly increased effectiveness of our psychiatric methods and skills, have had some very definite effects on the practice of medicine.

1. *The usefulness to and consequent increasing acceptance of psychiatry by medical people:* This is clearly demonstrated in the federal medical programs—in the military organizations, in the public health system and in the Veterans Administration. Prior to World War II, the recognition of the need for psychiatry in the army and navy was minimal. The Public Health Service did have a mental hygiene section beginning in 1929 but its activity was limited to the national problem of narcotic addiction. The psychiatric casualties of World War I were

in the hospitals of the Veterans Administration but for the most part rarely received more than custodial care.

During World War II, psychiatry gained stature so that it could operate on the same level with medicine and surgery in the army. This was true in the Surgeon General's Office and throughout the entire medical service—in the theatres, the armies, the service commands and in general hospitals. The significance of this development is emphasized by the fact that this system has continued as the method of organization and function in the armed forces since the war. In the Public Health Service, there is now a multifaceted mental health program, greatly expanded by the Mental Health Act of 1946. The psychiatric services of the Veterans Administration have been very greatly strengthened, with psychiatric sections in all general medical and surgical hospitals.

2. *Medical Education:* One of the most gratifying results of the recognition of the importance of psychiatry has been the very fundamental change in our medical school curricula. Prior to the last war, most of the Class A medical schools limited the teaching of psychiatry to a maximum of 30 to 60 hours, usually during the junior or senior year, consisting of a few lectures and demonstrations of the various types of clinical entities in a nearby state hospital. One of the experts on medical education, Alan Gregg, pointed out the need for a change (7). He stated "Perhaps the most desperately and thoroughly proven of all lessons from the war was that our medical schools had been giving grossly inadequate training in psychiatry. Their graduates, as a rule, misunderstood, ignored, and undervalued psychiatry. . . . There should be a major revision of medical education, for only a radical change will provide, in the education of the doctor, the opportunity for adequate training in the psychiatric care of human beings for a full and happy life as well as a symptom-free existence."

Since the war the majority of the medical schools have increased the time allotted to psychiatry up to three to five per cent of the total hours in the curricula, i.e., 200 to 500 hours during the four years. Instruction is given in each year. This is still too little time, but fortunately the more progressive schools now arrange for the permeation of the psychiatric point of view into the teaching of all medicine and surgery. In fact, in many instances, psychiatry is taught on the medical or surgical wards, and in the general outpatient clinics. Thus to some degree, the deficiency in the preparation of the average doctor in terms of understanding the personality and the emotional forces in disease is being corrected.

3. *Extension into General Hospitals:* Another evidence of the influence of psychiatry on medical practice is the increasing number of general hospitals that include a psychiatric division or section and general medical clinics that include one or more psychiatrists. As I indicated in my opening remarks, Mt. Sinai Hospital is an outstanding example of this relatively new development in the practice of medicine. The idea of the inclusion of a special section for mental illness in a general hospital is very old: in the founding of the Pennsylvania Hospital in 1752, special provision was made for the "insane." But it was not until 1902 that the second such provision was made in a general hospital, in Albany. In 1950, there were still only 279 general hospitals out of a total of 4761

that had adequate in-patient psychiatric service, providing for less than one per cent of all psychiatric beds (8).

4. *The Development of the Psychosomatic Emphasis* in medicine is another important evidence of the impact of psychiatry on the understanding and treatment of illness. Whether or not one likes this term, the fact remains that the renewed emphasis given to its use by the formation of an association and the publication of a journal,* has called the attention of many physicians to the fact that emotions can and do influence any disease process. The concept of psychosomatic medicine should not be applied to a specific group of diseases of undefined etiology but rather to a point of view that every illness has somatic and psychic components, the latter too often being ignored. There have been many surveys which indicate that at least 50 per cent, and perhaps even a higher number, of patients who consult the average physician in his office present no organic pathology. Further investigation of most of these patients invariably reveals important emotional factors in the incapacity. Furthermore, emotional disturbances account for 25 per cent of all admissions to general hospitals (8). Perhaps equally important is the increasing awareness of the significance of the emotional component in the diagnosis and treatment of organic disease. For the best practice of medicine, it has become essential that every physician be able to recognize and have the skill to handle the emotional factors, whether in a case of amputation of a breast or an instance of poliomyelitis with threatened or actual crippling. Nor can the physician ignore the potential emotional upheaval of the family of such patients.

The trend in the changing attitude of physicians is illustrated by recently coined terms and phrases urging the doctor to concern himself with the total individual and not merely with a set of mal-functioning organs, for example: "Treat the person and not the disease." "Study the individual as a whole." "Regard the patient as a social unit, not merely an anatomic-chemical mechanism." "Practice comprehensive medicine."

Another evidence of a change in attitude of physicians is shown by the increasing dissatisfaction with the inadequacy of a system of nomenclature that was based on an anatomic-physiologic-chemical or mechanistic conception of disease as localized in one part of the individual or affecting one bodily system. Confusion is confounded when the neurologist looks at the patient with his telescopic lens, the internist with his, and in turn the hematologist or the pathologist with theirs. It is a fallacy to believe that one can describe the total picture of incapacity of a social-psychological-biological unit strictly in terms of cellular changes in one small part of him. But to do otherwise is difficult. My brother presents the problem as follows (9): "What shall we call the 'disease' represented by a man who has always been frail but has worked very hard to support his widowed mother, did not feel he could afford to get married, buries himself in the details of a complicated job, develops paralyzing headaches, loses time at the office for which pay is deducted from his wages, worries about this so much that he loses sleep and begins vomiting after each meal? Just to make it complicated he has a

*The American Society for Research in Psychosomatic Problems. The journal is called *Psychosomatic Medicine*.

lukocytosis and an enlarged spleen. Does not such a case defy diagnosis? . . . Even in the simplest cases it seems . . . misleading to make a diagnosis in the old fashioned way. A middle aged puritan spinster appears in my office with a chancre on her lip. Isn't this a simple diagnosis? I don't think so. Nor would you if I told you the circumstances of how she acquired that chancre, whom she acquired it from, how she happened to select that type of man, or why she had permitted him to kiss her. Her sickness cannot be accurately diagnosed as just primary syphilis. She did not come to me because of it. What she came to me for was a more serious thing. She was so depressed about the implications of the infection that she now wanted to kill herself. What is the name of that disease? . . . What is the diagnosis in a patient who has coronary symptoms whenever he takes his wife to a party? or in a woman who has migraines on the weekends that her son is home from college? What kind of arthritis is it that becomes activated with each quarterly meeting of the Board of Directors?"

The significance of this changing attitude—primarily the result of the impact of psychiatry on medicine—has been to emphasize the fact that every patient is a social being whose psychological and emotional life is very much a part, if not the most important part in many cases, of a total reaction that might include pneumonia or appendicitis. "Clinicians are coming to regard disease more and more in terms of a disturbance of the total economics of the personality, a temporary overwhelming of the efforts of the organism to maintain a continuous internal and external adaptation to continuously changing relationships, threats, pressures, instinctual needs and reality demands" (9).

We can anticipate further effects of the impact of psychiatry on medicine in the future. There is every reason to assume that the body of psychiatric knowledge will continue to grow and that this knowledge and skill in using it, will become more and more helpful to the practitioners of medicine regardless of their specialization. Equally as important as this knowledge and skill in using it, is the point of view so essential to every competent psychiatrist—the holistic concept of the personality. This means that the patient must be studied not only as an anatomical-physiological-chemical unit but also as a psychological unit, and a social unit. Psychiatry is in a very real sense "comprehensive medicine." Its investigation can never be limited to a particular set of organs. The physician with a psychiatric point of view can never look at his patient as being merely a case of an abscess of the liver or a gunshot wound of the femur. The other specialties of medicine tend to deal with parts of a personality—the chest or skin or bones. But psychiatry must encompass not only the pathology of the individual's physical being but also the pathology in his psychological life and in his social environment. If and when this point of view could be inculcated into medical students, one might expect a major revision in attitudes and procedures in the practice of medicine.

THE IMPACT OF PSYCHIATRY ON SOCIETY

What if any influence has psychiatry had on society? On our culture? On our daily living? Any one person's answer to these questions depends on his ex-

perience and his impressions, for as yet there are relatively few generally demonstrable facts. Perhaps one might question the reasonableness of this query. For instance, what would one expect in the way of an answer if one were to examine the impact of orthopedics or surgery on our social living? On the other hand, if I am correct in my point above, that psychiatry is a form of and perhaps the only speciality of comprehensive medicine, one might expect it to have made some impression. It does have a greater potential universality of applicability than any other medical speciality.

Many social problems are related to a poor state of mental health. They exist to a greater or less degree in at least some sections of most if not all of our communities: inadequate housing, forced unemployment, labor-management strife and strikes, prejudice and discrimination, inadequate medical care, invalidism, the neglect or rejection of the physically and/or mentally handicapped individual.

Because these social problems create or are caused by mental or emotional upsets, they present various challenges to workers in the field of psychiatry. Constructive social forces should reduce the number and seriousness of these problems. Instead, most of them are growing. As a psychiatrist I believe that our knowledge and skill can contribute, at least in a small degree, to their solution. A desire to help should not be misunderstood. Psychiatrists do not have *the* solutions for these problems. But we do assume that the knowledge of personality structure and the factors that produce maladjustment in the individual and therefore in the social group, might throw some light on the etiology and the treatment of these disorders of society.

As we look about us we can see too many devastating social problems—devastating because they cause unhappy, unhealthy and ineffective living for so many of our citizens. If more of us were psychologically mature and would make it our urgent business, we might solve at least some of these.

First, of course, it behooves us to know just what they are, their extent, and whether they are increasing or decreasing. Many problems of individual behavior related to personality disorders are caused or aggravated by cultural or social factors and show up as criminality, narcotic addiction, alcoholism, suicide, delinquency and, in many instances, divorce.

To discover the extent and rate of increase or decrease, we should look at what the records show about life in America at the moment:

Statistical studies predict that one out of twelve children born each year will at some time during his life suffer a mental illness of sufficient severity to require hospitalization (10).

The last report from the Federal Bureau of Investigation reported 1,750,000 serious crimes committed the previous year—an all-time high (10). It is estimated that crime costs us between ten and eighteen billion dollars a year.

About 50,000 people in America are addicted to narcotics (10). This figure is regarded as an extremely conservative estimate.

It is estimated that there are about 3,800,000 problem drinkers in the United States, 950,000 of whom are people with severe chronic alcoholism (10).

About 17,000 American citizens commit suicide each year. Suicide ranked

5th as a cause of death among males between the ages of 15 and 44 for the years of 1936-1950 (11).

About 265,000 children between the ages of 7 and 17 are brought to juvenile courts each year—1.2% of approximately 22 million children in that age group (10). We have no estimate of the number of children with behavior problems who never reach the juvenile court.

For every four marriages a year there is one divorce (10). A divorce may or may not have been caused by an emotional illness, but always it creates unhappiness and, if there are offspring, a broken home.

Those of us who care cannot limit our survey to these wide-spread social problems. We need to have even greater concern for the lives of the "average" individual—the so-called "normal" individual. All of us are aware of the daily tensions under which we live. We are familiar with the stresses of life brought about by the rapid tempo of living, the increasing competition, the threats to one's security—economic, social and personal. Psychiatrists feel these forces in their own lives, and see them at work in the lives of their patients. But in any attempt to help toward the solution of social problems, they are confronted with limitations. First, their experience is restricted chiefly to working with individuals and the current demands for help from troubled people is far in excess of their ability to deliver it; second, as yet the knowledge of effective methods to prevent mental ill health is minimal.

One great field for activity in the near future is the development of preventive measures—techniques that will strengthen psychologic supports and reduce stresses. Psychiatry, like every medical science, must progress through three stages of evolution—first, the identification and description of pathology; second, the development of treatment measures; and third and finally, methods of prevention. Psychiatry is only entering the preventive stage in its evolution for, as I have indicated, the whole science is still so very young.

The field of preventive medicine has in many ways had perhaps the greatest impact on society of any branch of medicine, in terms of sanitation, food inspection, water purification, sewage disposal, epidemiology. It is surprising that in its development over the last 100 years, preventive medicine has only very recently begun to include mental health. The textbooks in preventive medicine still do not discuss mental ill health. Only four of our 12 schools of public health now offer some course or courses in psychiatry.

Under the leadership of the U. S. Public Health Service, we have begun to make faster progress. With the passage of the Mental Health Act by Congress in 1946, some, though as yet inadequate, funds have been made available for psychiatric training, research and community services. Under this last category, many states have set up programs. Some states are using the funds chiefly to assist in the development of community clinics; some provide informational and educational services, a few have instituted mental health workshops. As indicated, the monies as yet available are inadequate—far less than for cancer or heart disease—but very good progress has been made.

Having introduced the discussion of the impact of psychiatry on society in

this negative fashion—primarily to emphasize the need for a much greater one—let us examine some specific areas of social living and the relation of psychiatry to them.

THE IMPACT ON THE FAMILY

Psychiatrists, as a preliminary step in diagnosis, must study the family relationships of every patient. Whether through first hand contact or secondarily through the patient's description of his family, the understanding of that unit is essential to the understanding of the patient. Family life and structure is a major concern in the practice of psychiatry.

It is important, in terms of mental health, to try to discover what is happening to the American family as a unit and the changing roles of its members. What is the significance of one divorce for every four marriages? There is a mental health angle to the fact that nearly 2 million of the 19½ million women in the civilian labor force have children under 6 years of age (12). The type of home and the kind of family life, undoubtedly have a direct relationship to the absence or existence of delinquency in the children. The migration from rural to urban communities presents certain mental health hazards. No thoughtful person can remain unaware of the distractions and the demands upon the family which are created by so many groups and factors in our daily lives. It is always the family that must do the adjusting to demands from the school, the job, the church, the state, the community or the neighborhood. Unfortunately, psychiatrists have been and still are far too busy trying to take care of an increasing case load of emotionally upset individuals to give more than passing thought, except in the lives of their individual patients, to the removal of those hazards which they know so well to be prime factors in causing mental illness. Many individual psychiatrists, and in a small way some groups, have given counsel and support to lay agencies, like the National Council of Family Relations, the Association for Family Living, the White House Conference on Family Life.

Perhaps psychiatry's most important contribution to the family has been the discovery of the all-important role that the early family situation plays in the development of personality. During the formative years of infancy and childhood the foundation is laid in the individual for good or poor adjustment. The seeds of mental illness or mental health are planted in these early years.

Psychiatric findings have high-lighted some helpful mental hygiene guides for parents—the importance of: the child's identifying with the appropriate parent, helping the child learn to accept frustration, to test reality, to learn how to relate to people, and giving an opportunity to the child to learn how to love. Such information has been widely disseminated, and increasingly so, through books, syndicated news columns, study groups, health workshops, college and even high school courses. An extremely significant impetus to the education of the public in this area came from The White House Conference on Children of 1950, devoted primarily to a study of the mental health of the child. Through state committees, this commendable effort is still being carried forward. At national, state and local levels, psychiatrists have played an important role.

The practice of psychiatry has pointed up many of the problems in other so-called "critical" periods of life affecting the family. Thus, it has contributed in a major way, both to the understanding and management of the two *major problems of adolescence*—the emancipation from the home and the psychological reactions of physical maturity. These contributions have been passed on to large numbers of parents through popular presentations on this subject which lean heavily on the knowledge gained from psychiatric study. Several of the more popular ones have been written by psychiatrists.

A rapidly growing development of great significance to the family is *pre- and post-marital counseling services*. Workers in this field include psychologists, sociologists and clergymen, as well as physicians. A few psychiatrists devote their full time to this special interest, and many others include it in their clinical practice.

The president of the National Association of Marriage Counselors is a psychiatrist. The only two training programs for marriage counseling have been established in connection with psychiatric centers.

The process of aging is of more than passing interest to psychiatry. For the first time in our history, senile psychoses and cerebral arteriosclerosis (coming with old age) make up the largest single group of mental illnesses admitted to our mental hospitals. We can do very little for these sick individuals, numbering now more than 26,000 persons a year—more than a fourth of all of the first admissions (13).

Quite apart from the need of elderly persons for psychiatric institutional care, are the very real psychological problems of all of us which arise from the process of growing old. On the basis of current statistical studies, we can expect these to increase. In 1950, the average length of life of the average individual in this country was 68 years, 28 more than at the time of the incorporation of Mt. Sinai Hospital in 1852 (14).

Social security pensions are by no means the sole solution of the problems of aging. The wide-spread practice of forced retirement, when an employee may still be quite competent, results too often in disastrous effects on that person's mental health—producing a sense of dependency, uselessness and exclusion. Many of the larger industrial concerns are wrestling with this problem as are groups of thoughtful citizens. Clark Tibbits (15) has reported on the deliberations of the National Conference on Aging under the title of *Aging: Implications for Public Health*. It is a public health problem but he very well could have reported on "Aging: Its Implications for Mental Health." He elaborated on the need for a favorable environment for older people, the necessity for them to have an opportunity to work and to feel useful, the desirability of opportunities for creative activity in recreation, and of happy and satisfying living arrangements—all of which are primary factors in maintaining mental health at any age.

IMPACT ON OUR EDUCATION SYSTEM

One might ask what psychiatry has to do with American educational systems. Few, if any, intelligent individuals would disagree with the statement that

the general education of a child is an extremely important factor in his mental health. Its absence may be a direct cause of mental ill health. For many people America is the land of opportunity, but educationally this is not true for others. Norton and Lawlor pointed this out in a very dramatic fashion (16).

3,000,000 adults living in the United States have never attended any kind of school.

10,000,000 adult Americans have had so little schooling that they are virtually illiterates—they cannot read and write well enough to meet the demands of modern life.

Half of the brightest and most talented youth of the nation leave school prematurely—before they have had the kind and amount of schooling which would be justified by both their ability and the demands of our way of life.

2,000,000 children, aged six to fifteen, were not in any kind of school in 1940—and this number was substantially increased during the war.

The schooling provided millions of American children who are in school is so inferior and brief that it leaves them unprepared to meet the demands made upon them as citizens and as individuals.

Psychiatrists have begun to contribute to our educational programs in several different ways. First, they urged the value of improving student mental health. Beginning in 1920, universities and colleges began including courses of mental hygiene in their curricula. Psychiatrists have gradually been added to the medical staffs of the student health services. At present about 20 universities have the full-time assistance of one or more psychiatrists. One university has three full-time psychiatrists, assisted by seven full-time associates. An increasing number of Boards of Education, both in metropolitan and smaller communities, employ psychiatrists, for part or full time, to work in primary and secondary schools.

These efforts have paid off well in terms of direct help to students—those who have difficulty in studying, home problems, and minor as well as major personality problems. The need for such help is suggested by the fact that of 1000 students who reach the 5th grade, only 453 will still be in school at the 12th grade. Survey reports leave no doubt that personal maladjustment is the major cause for dropping out of school (17).

Other areas of the educational process to which psychiatric knowledge has contributed in some degree include defining the goals of education, teacher training and curriculum planning.

Many alert educators very well know the need for better teacher selection, improved motivation, more effective ways to help the problem student, more specialized types of education for specific kinds of handicapped students. The theme of a major section of the National Education Association, the Association for Supervision and Curriculum Development, for its annual meeting in 1950 was "Mental Health for Better Living." The Year Book of that organization for 1950 was entitled "Fostering Mental Health in Our Schools." There is an increasing acceptance by many educators of the idea that the goal of education should be to help the child solve the problems of social living and not merely to acquire knowledge. The Educational Policies Commission of the National Edu-

cation Association has been stressing for nearly ten years the value of a program referred to as "Life Adjustment Education", to include in the curriculum courses in home living, vocational and civic life, leisure time, physical and mental health.

One group of psychiatrists has made a special study of some attempts to include mental health principles in the curriculum of secondary schools. They investigated and reported on some interesting experiments in educational institutions in various parts of the United States. One of these experiments was aimed at helping the child become more aware of the social graces. A second consisted of a weekly student discussion of character traits and personality reactions. A third and extremely interesting experiment endeavored to make the subject matter of the curriculum dynamic and socially meaningful rather than merely to teach isolated static facts (18).

IMPACT ON BUSINESS AND INDUSTRIAL LIFE

Unfortunately the influence of psychiatry on business and industry has been minimal. There has been, however, a beginning. For some years psychologists have contributed in extremely important ways, some times with the help of other social scientists, by wrestling with the personnel problems of industry. The Department of Industrial Relations of the University of Chicago under Dr. Robert Burns has developed some remarkable aids for industry to survey employee attitudes, employee performance records, and has prepared presentations of elementary economics for employees. The use of vocational tests has gained increasing acceptance. Tests for the evaluation of personnel are being used by many business and industrial concerns. But the need for and the role of the industrial psychiatrist is still vaguely understood although now well defined (19).

Only 15% of 62,000,000 workers in America have an in-plant health service, perhaps because 70% of these people are in plants with less than 500 employees. Only 5% of the smaller organizations maintain their own health services. Of the larger industrial organizations, only a very few have utilized psychiatrists in their health programs. Even these few, however, have demonstrated the contribution psychiatry could make through emotional first aid stations, supervisor training, and reviewing personnel and selection policies in terms of their mental health and moral aspects. Supporting this psychiatric opinion is a statement from the National Association of Manufacturers that a well-planned medical program, including a complete mental hygiene unit, can effect a 45 per cent reduction in accidents, a 63 per cent drop in occupational disease, a 30 per cent reduction in absenteeism, and 27 per cent reduction in labor turnover (20).

An increasing number of progressive executives in industry and business are conscious of the importance of human relations in industry. "Human engineering," "human leadership", "human management" now encompass more than production efficiency. The emotionally sick executive, high labor turnover, problem employees and alcoholism are costing industries, and therefore consumers, unbelievable sums of money. One fact of interest is that 60 per cent of the dismissals in industry are necessitated by personality problems that have no relation to technical competence. The original study first demonstrating this

fact, was carried out by a psychiatrist, Elmer Southard, in 1919 (21). His findings have since been confirmed by several similar studies.

The statements of some of these executives are significant. Lewisohn in his stimulating book on "Human Leadership", written shortly before his death, stated, "The problem is largely that of securing a new emotional orientation towards the subject of human relations in industry on the part of employers and executives. Along with pride in the size of their plants, the quantity of their output and the amount of their profits, they must find some pleasure in boasting of the excellence of their methods of human organization." (22) Clarence B. Randall, the president of Inland Steel Company, recently expressed the same thought in a forceful way, "We speak glibly of the importance of personnel relations in industry, yet where are the corporations that have made important grants to the social scientists and the universities for research into human behavior? We have learned a great deal about what causes friction in machines, but have not sought to learn what causes friction between human beings. We know what causes heat when metal meets metal, but have not demanded to know what causes heat when man meets man. Physical research has taught us what lubricants to use to reduce friction and heat in mechanics, but we have established no social research programs to determine what lubricants will best reduce friction among people. What do we know about the whole question of mass behavior which breaks out in the riots around our gates, or the broad problem of motivation in human conduct?" (23)

With such attitudes developing, even though psychiatry has done little for industry to date, at least the green lights are on.

IMPACT ON THE MILITARY

Psychiatry has had considerable impact on our military organization, or perhaps more correctly in our military organization. It is one field in which I am sure that psychiatry has had an influence, and a major one, in shaping the present picture.

The lessons that were learned in the attempt to apply psychiatric knowledge in World War I were lost long before World War II began. The unpleasant facts are that when the second world catastrophe broke out, there was no real comprehension of and almost no preparation for the inevitable psychiatric casualties that would result. During the interval between the wars for many years there was no psychiatrist at the headquarters of the army—the Surgeon General's office. When one was included, his only function was to review the officer retirement board papers. The only reference to psychiatry in all the voluminous army regulations had to do with the disposing of psychotic patients. Even as the war began and new hospitals were built all over this country, the only preparation for psychiatric casualties was the construction of ill adapted and unattractive closed wards that looked more like jails than parts of a hospital. At the beginning of the struggle the only positions of assignment for psychiatrists were in those hospitals. There was no official recognition of the desirability of having these professionally trained individuals on duty with soldiers in the field. There was no

plan for treatment, either in the hospitals or near the front lines for combat casualties. All of the clinical psychologists were in the Adjutant General's department and the army had never commissioned or utilized social workers except as provided by the Red Cross.

Without prolonging the story which can now be told in the past tense, suffice it to say that all of these deficiencies were in some degree corrected during the course of the war. It is with great pride that those of us who had a part in this enterprise have stood by to see psychiatry continue to play its important role in both the Army and the Navy. Profiting by the lessons learned during World War II, there is an even greater efficiency and effectiveness of treatment of the psychiatric battle casualties in Korea. This is gratifying to see.

All of us in civilian psychiatry are proud of the role that psychiatry was permitted to play during the war. To do so, it had to overcome all the obstacles of ignorance, firmly held misconceptions and prejudices that one meets in civilian life and, in addition, red tape and even in a few instances bull headedness.

IMPACT ON OTHER AREAS OF COMMUNITY LIVING

Community psychiatric clinics have developed only during the last thirty years. The Child Guidance Clinics, which were started under the aegis of the Commonwealth Fund in 1920 as pilot experiments in several metropolitan communities have been continued in every case, and many new ones begun. But there are still some states with no psychiatric clinics. At the present time, there are about 600 community clinics, approximately half of which are full time. About 40 per cent of these are operated in connection with hospitals, 120 in general hospitals and about an equal number in mental hospitals. According to the best estimates, on a population basis, there should be at least 1800 full-time clinics (24).

These community clinics are the front line of treatment and prevention in psychiatry. It is the firm conviction of those of us in this field that were psychiatrists able to see patients earlier in the development of their emotional difficulties, treatment could be far more effective and require a shorter period of time. In addition to therapy, these clinics are the center of mental health activity in the community. Not only do they furnish counsel and advice to people who are ill but also to those threatened but not yet incapacitated. They also serve as sources of information, provide leadership for citizen groups, frequently act as consultants for social agencies, school systems and the court. These clinics have probably been the most potent psychiatric influence in our communities.

One cannot ignore the *impact of the state hospitals* on the community but unfortunately, for so many years, they had a very negative effect. Much misunderstanding about psychiatry grew out of the fact that state hospitals were incapable of doing the job they were assigned to do. Many were truly Snake Pits. Although there have been very marked improvements in them, most state hospitals are still a blot on our social escutcheon. On a national average, one physician must assume the care of 258 patients. About three out of every four state mental

hospitals report over-crowding, with 37 per cent of them over-crowded in excess of 30 per cent (10). Nearly 60 per cent of the patients that enter them, spend the rest of their lives there!

There are, however, signs that the social conscience is awakening through the help of some militant journalists, the far visioned leadership of the governors of a few states, increasingly active citizens groups, and the energetic efforts of the American Psychiatric Association. Extensive improvements have been made in a few of our state hospitals.

Psychiatry is having an increasing impact on our *courts* as more of them seek the help of psychiatric counsel and guidance, for both adult criminal and juvenile cases. In a few of these, there are full-time psychiatrists. Undoubtedly there would be many more if well-trained psychiatrists were available.

Several metropolitan *churches* maintain psychiatric clinics. One has developed an organization in which the minister and the psychiatrist work together in their counselling of troubled people—the Marble Collegiate Church here in New York. A journal is now published, "Pastoral Psychology," which has an editorial board composed of psychiatrists and members of the clergy.

Psychiatry is beginning to play a small role in the field of *recreation* and leisure time. A very active committee of the American Psychiatric Association has contacted and offered help to many groups in this field. A section was formed this last year in the National Recreation Association for workers in recreational therapy in hospitals. The relationship between mental health and recreation is perhaps most clearly seen in many studies of delinquency which indicate a much higher incidence in so-called under-privileged areas where there is a conspicuous absence of recreation leadership and facilities.

One could hardly review the influence of psychiatry on community living without paying great credit to the *mental hygiene movement* begun by that remarkable person Clifford Beers, in 1909. Most of our states and a great many of our communities now have groups of citizens which are banded together for the sole purpose of improving mental health. A tremendously forward step was taken last year when the National Committee for Mental Hygiene which had been carrying on for 40 years, fused with two other lay organizations having very similar purposes to form the national Association for Mental Health. This group assists the state and the community mental hygiene societies with their programs of providing public education about mental health and ill health, influencing the care provided mental patients in the state institutions, working for legislation for better commitment laws and other mental health measures, conducting study groups for parents, teachers and other leaders, and fostering community mental health clinics. It is the hope of those of us connected with this organization that it may be able to give the leadership in mental health that has been so excellently given for cancer by the American Cancer Society, for infantile paralysis by the Poliomyelitis Foundation and other similar national health efforts.

IMPACT ON THE AVERAGE MAN

How much of an impact has knowledge of mental health and illness had on the average man? Short of psychiatric treatment, has the knowledge from this science helped Mr. Everyman to maintain and improve his mental health? One has to answer by saying that we simply do not know. As a psychiatrist I feel that it has to some extent but not nearly enough.

There has been some effect. Were it not so, there would not be even the auditoriums full of militant citizens here and there in communities across this country who come to learn how to work actively for better community facilities, better state hospitals and better schools—and also, for solutions to social problems in terms of better mental health. Were people not informed about the possibilities of help, those of us who practice this specialty of medicine would not be swamped by the many, many requests for talks and advice from individuals and groups, requests that far eclipse the ability of our present manpower to meet. These requests come not only from individuals who are in trouble but from organizations of all types—business and industrial, legal, educational, religious and many, many others.

There is much evidence that more and more people are cognizant of the existence of psychiatry and its knowledge does offer some new hope for more satisfying living. Not so long ago *Collier's Magazine* employed the public opinion analyst, Elmo Roper, to survey the city of Louisville, Kentucky, to determine the extent of public understanding of psychiatry and mental illness. The story as reported by Albert Maisel (25) indicated that almost everyone interviewed—some 4,000 citizens—were “in favor of psychiatrists” though much confusion existed as to when one should be consulted. It was believed that this survey demonstrated that the public wanted both more psychiatric services and better ones. It indicated a wide acceptance of psychiatry but revealed a lack of understanding of the need for it in specific cases.

Another evidence of the widespread interest in psychiatry is the attention paid by the experts in mass communication—writers for newspapers, magazines, radio, television and the screen. It is probably correct to assume that this group knows better than any other the more important interests of the American Public. This new interest undoubtedly grew out of the war when 1,700,000 men were rejected because of personality problems, and another 700,000 were discharged from the services for the same reason. Psychiatry became news. Since that time it has continued to be news. For better or worse, the public has and is receiving an extensive education about personality, psychology, psychoanalysis, mental institutions, treatment measures and related subjects. It is significant perhaps that the *Snake Pit*, the moving picture produced by Twentieth Century-Fox four years ago brought in an all time high of box office receipts, despite the fact that the original opinion of the top-flight producers was that it would be an enormous economic loss.

With all of the evidence of a major impact by psychiatry upon Everyman, there is much counter-evidence that its effect has not been great enough. In the light of the mounting statistics of admissions to mental hospitals, delinquency,

crime and other evidences of maladjustment our national mental health remains the number one health problem. Otherwise well informed people have little or no knowledge of mental health principles. Nor can one live in this turbulent world and be unconscious of the hostilities that surround us on every side as revealed by the countless evidences of selfishness, greed, suspicion and insecurity. Even yet stigmatization of psychiatric patients is the rule, whether due to fear or ignorance or hostility or some other form of self-defense for the accuser.

As a psychiatrist I dare speak for all of my confreres as to our hope regarding the impact of our knowledge on the average man. Our ultimate aim, as is the aim of every physician, is to make our services increasingly less necessary. Everyman is our chief target. We believe that the knowledge of psychology and psychiatry can give a scientific basis for understanding the behavior of the individual—ourselves and those about us. As Dr. Alan Gregg once wrote me in response to my question as to what psychiatry had to offer, "Psychiatry leads to a life of reason. It explains what must otherwise excite fear, disgust, superstition, anxiety or frustration (26)."

We in psychiatry believe that as a therapeutic science psychiatry can bring surcease to troubled souls; it can diminish and extinguish fears; it can increase one's badly needed sense of security; in short, it can increase one's satisfaction and efficiency of living. We want to see it become the tool of every physician.

And further, we believe that psychiatry has not only provided therapeutic aids for mental illness but it has delineated the goal of emotional maturity—the objective of a healthy personality. The psychologically mature and therefore mentally healthy person is able to deal constructively with reality at its worst; to find more satisfaction in giving than in receiving; to be relatively free from tensions and anxieties; to be a creative contributing person; to possess the ability to accept frustrations for future gain; and to learn to profit from experience. These, the psychiatrist believes, are some of the qualities of the mature person.

CONCLUSION

In attempting to be constructive in the presentation of this evaluation of the impact of psychiatry on medicine and society I want to express also the humility that I believe most of us in psychiatry feel about our accomplishments to date. We do not believe that psychiatry has *the* solution for all social problems. We know that it does not even have the answers to the many questions about severe types of mental illness and maladjustment. Nor do we over-estimate the impact that psychiatry has had on our civilization. In fact, we regret that it has been so insignificant—we regret this because we believe that it has so much to offer. Psychiatry may have become of age as a medical science but most psychiatrists feel that it is just emerging as a social science.

We do believe that psychiatry has a very solid base. We do feel that it has made a considerable contribution both to medicine and society. We believe it promises much if it can overcome other major obstacles in the path of its further development. In closing I would like to share these with you, believing that the better known they are, the more help we will obtain in their solution.

Our first and greatest obstacle is the provision of qualified personnel. Trained manpower is *the* bottleneck in the further progress of psychiatry. We have approximately 6,000 psychiatrists, only half of whom have been certified. On the basis of population needs we should have 20,000 well qualified psychiatrists. All the training institutions of the country are turning out about 500 new psychiatrists a year. This means that with the present production, it will take 28 years to meet our present requirements. Along with the shortage of psychiatrists are parallel shortages in the various categories of our associated workers—clinical psychologists, psychiatric social workers, psychiatric nurses, adjunctive therapists and psychiatric aides.

The second great obstacle is the lack of knowledge that can be gained only from research. Despite the enormous public interest in psychiatry, as Kubie (27) has described our plight, "Our research programs are starving to death for lack of financial support." Less than five million dollars in public and private funds were available in 1951 for basic studies on the cause, treatment and prevention of mental illness. Had the per patient investment been equal to the research funds available for study in poliomyelitis, tuberculosis or cancer, this would not have been five million but thirty-three million dollars. Incidentally, the government allotted \$31,000,000 for control and research in hoof-and-mouth disease in 1950.

The third obstacle is the insufficient understanding of mental health and mental ill health on the part of the public. Yes, there is a wide popular interest but this interest does not indicate adequate understanding. It has not reduced the incidence of mental ill health. It has not provided sufficient financial help.

Mental ill health is the number one problem in America in terms of the number of patients afflicted, the economic cost and the tax burden for every one of us, the proportionate shortage of personnel and the lack of funds for research. There is a great need for men and women of stature and vision who will give leadership and substance to this hinterland of health, a field that gives great promise for bringing more happiness to men's lives and peace to many troubled personalities.

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MEDICINE AND SOCIETY: IMPLICATIONS IN THE ATOMIC AGE

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Speakers on the atomic age are rather routinely expected to project their thoughts into the future, dwelling only secondarily upon the past and the present. This leaves free play to the imagination. Such, however, is the inertia of man's imagination that he is almost certain to go off at a limited number of tangents when he does research or talks about the future. This tendency can even be observed in science fiction; and so I trust the author of a learned discourse on this subject may be forgiven if he falls as short as would an electrician predicting, 30-odd years ago, the future of the vacuum tube. Other speakers have been able to view the next centennium with a broad look at the last one. My own view can go back only one-tenth of this period, since next Tuesday is the decennial of controlled atomic fission.

Some things can be predicted more easily, and with a higher probability of fulfillment, than others. Developments based on the application of knowledge and skills already at hand are fairly predictable, insofar as they are subject to planning. Other developments are not subject to planning; they grow out of patient observations and thoughtful analysis and oftener than not are answers that were not sought to questions that were not asked. By the very nature of their unpredictability they open new doors in what have been blank, and perhaps unnoticed, walls; they are called basic. Thus some basic pre-war discoveries in physics led, during the war, to a rapid development in the high explosive field and into many further developments of peacetime importance. At the same time new tools have been developed, or given impetus, which should enable the advance in basic knowledge in physical and medical sciences to continue.

It seems to me that a consideration of medicine in the atomic age should include both applied and basic medical science. A discussion of the social climate in which science will have to operate is also pertinent, since in the streamlined age of research epitomized by the way in which atomic energy was achieved, not all of the changes in science and medicine are necessarily good.

Nuclear energy has had less immediate beneficial impact on the practice of medicine than some of the more sanguine prophets hoped. It goes without saying that the radioactive isotopes have important possibilities in the treatment of malignant disease, and that some of these possibilities have been realized in the extensive regular use of radioclements in medical centers. They have been especially well tried in malignant diseases of the blood, where radioactive phosphorus is in common use. This isotope deposits itself in the vicinity of bone and bone marrow, in other sites where blood cells are formed, and is taken up somewhat selectively by rapidly growing tissue. The radiation intensity in these areas is slightly greater than in the body as a whole so that radiophosphorus has somewhat of an edge over X ray treatment to the whole body. And so with many other applications which really represent improvements in well-tried principles.

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The really outstanding example of isotope treatment is that of cancer of the thyroid. Unfortunately, most of these tumors have lost the special capacity of the parent gland to absorb iodine, but in those cases where the malignant tissue does so, the radioactive isotope deposits itself in the tumor, including colonies of tumor cells throughout the body where the disease has become disseminated and hence unavailable to surgery or conventional radiotherapy.

Some comparative figures may be of interest here. In one reported case, while the normal thyroid received a radiation dose of at least one hundred thousand roentgens, the somewhat less iodine-hungry tumor received about 6000, which is a respectable tumor dose but still only about 20 times the amount to which the total body could be subjected without acute radiation death. This points out the fact that for successful selective and eradivative tumor therapy, the concentration of a radioisotope in the tumor must exceed the average body concentration outside the tumor by a large factor, say between 20 and 100. We do not know of another instance where such a selective result can be achieved, but we have only scratched the surface as regards testing various isotopes and their compounds (particularly those of carbon and tritium) on various types of tumor. No compound seems to have been discovered in which carbon-14 becomes concentrated in any organ or tissue by a factor of more than 10 over the mean body concentration.

The use of isotopes as tracers in clinical investigation has shown great promise. In such measurements as rate of blood flow, or the outline of a gangrenous area we may take advantage of the fact that radioelements can be measured and located from a distance, and so they can be determined in the intact organism. Tumors may be localized where there is selective concentration of an isotope in the tumor as compared with surrounding tissues. This is often the case where phosphorus-32 is given, because of its selective localization, but owing to the slight tissue penetration of its beta ray (a few millimeters) it is not of great value where the presence of a tumor cannot be detected by inspection. Tumor localization has been rather successful in brain tumors, since many injected substances are more highly concentrated in the well-vascularized tumor than in the brain substance. It is erroneous to say that a brain tumor concentrates such substances to a high degree; the point lies in the low rate of penetration of most substances into normal brain.

Advantage has been taken of a peculiarity of certain isotopes which simultaneously emit two radiations in exactly opposite directions. Here it is possible to set up two counters so arranged that counting takes place only when both are activated coincidentally at the same moment. Using one of these isotopes with such a coincidence circuit, one can localize the source of radiation as being on the imaginary line connecting the two counters. Such a method can, theoretically at least, achieve localizations far superior to simple scanning of the surface of the head or of an operative field, where unless the tumor is close to the counter, only a very general localization is obtained.

It would seem clear from the foregoing that there is little chance of irradiating a brain tumor selectively for purposes of therapy by use of an agent which concentrates comparably in most normal tissues other than brain. A way around

that has, however, been discovered, in which a combination of directed beam therapy and selective localization of a substance is used. Slow neutrons are absorbed by all of the elements, and at the time of absorption the freed energy is released in the form of radiation, usually a gamma ray. The various elements and their isotopes differ enormously in the likelihood of this reaction: Thus, when a rock of average composition absorbs slow neutrons, a large proportion of them is captured by the iron and gadolinium and very few by many of the common elements. Those elements that are most likely to capture slow neutrons are said to have a high cross-section. Now, boron has a much higher cross-section than normal tissue constituents, and moreover, the energetic product of the capture is an alpha ray, which is biologically more effective than the usual gamma ray. The possibility was considered many years ago, before good neutron sources were readily available, that boron-containing dyes localizing in tumors might be useful if combined with slow neutron therapy. Such treatment of brain tumors (where much of the localization is gained by directing the slow neutron beam, and local selectiveness by the use of boron as a substance preferring the tumor to brain substance) is now being used at the Brookhaven reactor.

Volumes of dilution are commonly used in the determination of the several body water compartments, and measurements of blood and extracellular volume play an important part in clinical research. Using radioactive isotopes, one can go a step farther by measuring the actual amount of an element which exchanges readily with other atoms of the same element. It is now possible to estimate the total body sodium, potassium, and compounds such as uric acid in this way. Rates of utilization (and hence of production) of substances whose cycle lies normally within the body, the fate of drugs and trace substances, and so on, can be studied by tracer methods. Where such problems may also be attacked by chemical methods, it is still often true that the use of radioactive methods makes possible the estimation of much smaller quantities, and hence the study of toxic materials in non-toxic amounts.

One other potentially valuable tool is worth mentioning. As remarked above, slow neutrons are absorbed to various degrees by various elements. Frequently the absorption results in production of a radioactive isotope of the element, which appears in proportion to the quantity of the element present. Since the radiation decays in time, it may be possible to save the intact specimen and re-irradiate it to secure a further analysis. Activation analysis is most suitable for elements of favorably high cross-section and has been used successfully for iodine and gold in tissue. Because of the great variety of half-lives and physical characteristics of radioactive isotopes, many elements can be distinguished in this way; and in combination with chromatographic or other means of separation, highly definitive analytical results are possible.

Although this symposium is supposed to be of a general nature, I have troubled you about all of these details regarding the specifics of "atomic medicine" for the good reason that they point out some important generalizations. First, isotopes have an established part in modern diagnosis and therapy. Although we see no evidence of a real "break" in the sense of a nuclear development that will

have the same impact on important diseases such as cancer, as antibiotics have had on the infectious diseases, we can still foresee an acceleration in the steady progress continually accomplished through development of skill and experience in the use of new tools.

Secondly, all of this entails the spending of more money for the possibly diminishing return of the best possible practice of medicine. Much of the increase in the per capita cost of medicine can be attributed to the irreversible search for the best: for a return that is necessary and proper, yet increasingly costly. Some of the equipment in the atomic field is not too expensive, but the precautionary measures (the meticulous reasons for which I shall mention later) are.

Finally, if the break should come, and if it required not just an inexpensive agent such as an isotope, but a widespread availability of nuclear accelerators or reactors, we might then be presented with a staggering problem in medical economics. So far, advances in medicine have increased the cost of optimal care greatly, but not to an impossible extent. It may be fortunate that the new accelerators have not resulted in such absolute progress in therapy that they must be available at every hospital. If it turns out that devices of such magnitude should have an absolute value in eliminating cancer, we should really have a problem on our hands. Until such a millenium, the atomic age only adds more or less its modest share to the medical-economic stress that makes neither patients nor the profession exactly happy.

Medical personnel presents another problem. It is hard to know what part in the current shortage is played by increased utilization of medical care and what part by new areas of necessary specialization; but we have now reached the point where enough money is not available for the expansion of medical schools or for the creation of new ones.

Let us now turn to basic science, returning to the often repeated truth that this is the spring nourishing technological progress, or the money in the bank.

The atomic age has brought new instruments and new concepts. As far as medical research is concerned the instruments have until now played a greater part than concepts. But new techniques introduce new problems, and where there is wisdom in the handling of the problem, concepts follow. One example will suffice: that of the use of radioactive isotopes in basic biochemical research.

Growth has long been one of the more inscrutable biological problems; most of our present knowledge in this field centers around nutrition or is essentially descriptive. Fundamental knowledge of the nature and relations of growth and ageing is sparse, and the relation of cancer to other forms of growth, although understood in great detail in some areas which (judging by past progress) may be trivial, suffers from our lack of understanding of the basic underlying facts about growth in general. This truth has been given due emphasis by Dr. Weiss and I shall not pursue it further.

Through the insight of Schoenheimer and his school, even before the unveiling of the "atomic age" isotopic research had driven us to revise some of our concepts. Sound interpretation of isotopic studies taught that the living organism builds itself up, and maintains itself, through a continuous process of synthesis

and breakdown of chemical compounds hardly suspected by classical biochemistry. We are accordingly beginning to understand where much of the energy evolved in metabolism is used and to what purpose. Normal and abnormal growth, being primarily synthetic and endothermic processes, could hardly be understood in the framework of the older, degradative biochemical methods. In studying, quantitatively and dynamically, the synthetic component in its own right, we may well hope to find the key to the nature of the inexorable, if not necessarily efficient, process of malignant growth.

In the field of photosynthesis, where the process is perhaps simpler, or at least easier to isolate out, progress has been faster and no doubt serves as a prototype of the type of progress in understanding of growth that we may expect to see. Already we know important instances in which certain tumors differ in their synthetic capacity from certain normal tissues. What is more significant is the fact that, based on new concepts, students of cancer now look upon a tumor as a "trap" which holds on to certain substances it synthesizes and does not again release them in the normal process of exchange and turnover. What the master reaction is in this trapping process (or whether this is the right concept) remains to be known.

I shall not attempt further predictions in the basic area. Given new tools and concepts, while keeping the old ingenuity and imagination, one can predict much; but to predict what would be the height of vanity.

Nor do I care to say a great deal about the effect of the new basic concepts and their consequences on society. If I were endowed with a greater genius for seeing things in a glass sphere—if I knew, for example, whether such improvements in research would put us much closer to immortality—there would be a great deal to say.

The subject of radiation sickness is one of great interest and practical importance. Aside from the few myriad inadequately studied cases in Japan, almost all of our knowledge of the clinical disease has been gained by experimental work. If society is again confronted by it, it will again be on a large scale, and our studies of it will involve not only the nature of useful treatment, but a sort of logistic certainty as to what we should use and in what quantities. Burns and shock, the other mass wartime hazards, could be studied on separate cases and in small epidemics in peacetime life: but due to the respect we accord radiations, the interim clinical material is hardly available. As we become bolder in radiation and isotope therapy—remembering, for example, that proper iodine-131 treatment of thyroid cancer includes heroic total-body irradiation,—the treatment of radiation sickness becomes an essential adjunct to cancer treatment.

But what of the late deleterious effects of radiation? Since they are so delayed that their latency 1) approaches the life-span (as cataracts, leukemia, and tumors), 2) is identical with the life-span (for continuous irradiation at moderate levels shortens life moderately) or 3) greatly exceeds the life-span (referring to the production of recessive genetic changes) their study in man is too long an art, while in short-lived animals it requires an understanding of something I believe we know nearly nothing about, namely the basic physiologic meaning of

the different rates of aging in species so similar in their classical physiologic behavior as mice and men. I have already suggested that the atomic age has supplied a method of further studying this problem; now I shall refer to a rather unique reason motivating it.

The Atomic Energy Commission, which finds itself responsible for the conduct of most nuclear research and for the proper use of most radioactive isotopes, operates under an act of Congress requiring it to assume considerable responsibility for protecting the health of workers in this field, and of the general public where people might be exposed to radiations from its machines and products. Those of us who are in this business are accordingly being asked unanswerable questions, for example how much daily radiation exposure can be considered harmless. When one group made a serious proposal that the radioactivity of water coming from atomic energy plants should be kept at less than a certain amount, and this turned out to be considerably less than the natural radioactivity of the Mississippi River, of course the answer was simple.

The point is, however, that the whole atomic energy business has been pursued with a singular determination to make it completely safe, which has had no parallel in any other industrial or public venture. This has necessitated some serious considerations of problems in biology beyond the borderlands of our present knowledge and has entailed serious consideration of the concept of what man will tolerate as "safe enough" such as has not entered our thinking in regard to cigarette smoking or the possibly carcinogenic pall that hangs over our great cities. This aspect of the atomic age will have important repercussions in the social sphere as well as in basic medical science.

A word may be due regarding the much discussed genetic hazard of chronic irradiation. Here we have fairly good reason to believe that there is no threshold; or in other words, that any infinitesimal amount of radiation creates a corresponding infinitesimal probability that a germ cell will mutate. Some illustrious prophets of genetic doom have shown good cause that this is bad; that most mutation weaken the species and that an increase in their frequency will hasten its weakening as a whole. Perhaps this idea forgets the possibility that we may be where we are by evolution through mutation; that either the process of evolution is a downhill course or it is not (and I prefer not to take sides on that issue) but the most likely effect of irradiation is to accelerate it. Two other important factors are selection and inbreeding. There is no question but that we are reducing selection, or survival of the fittest, by advances in many fields of medicine—for it will soon be true that anybody may survive the procreative period; while it remains to be demonstrated that moderate inbreeding, as is true in many of the villages of Switzerland, has had really dire results. If, however, the frequency in the population of semi-lethal or deleterious recessive mutations is raised, inbreeding takes on a new significance.

If we are worried about sterility and semi-sterility, which are apparently the most likely results of radiation on higher animals, we may console ourselves by the thought that, under the moderate dosage we may expect to see, measurable effects may occur only after half a dozen or a dozen generations. This will take

us ahead in history beyond the next hundred years we have been speaking of today, and one wonders what the world and human race will look like by then. If the present population increases it may take care of many of our lesser worries. No matter how efficient we may become in the use of soil, perhaps the ultimate spectre, overshadowing by a large factor radiation, or smoke, is this increase in the population of the earth which keeps some parts of its surface happy only so long as technological advances in medicine and agriculture keep abreast of each other.

In any case, the atomic age will stimulate a realistic study of genetics and evolution in relation to man and his own problems; and this is certainly underlined by his unwillingness to endure any detriment in exchange for this particular technological advance.

If we are talking about our views concerning the possible bad effect of a little radiation on a few people, we must naturally wonder—not whether we are overdoing it, since we have set ourselves this goal—but to what extent a disregard of the rules of safety may have set the Soviet effort to secure atomic energy ahead, as well as the espionage that has so concerned us. For the health precautions are time-consuming and expensive. Possibly a thought such as this may also help to put some of our radiobiological-medical worries in their proper place.

I wish, in closing, to discuss the social implications for scientific advancement emerging from the industrial revolution in science. The atomic energy development is obviously only one aspect, but it is the best known, and represents the essence of a change which was bound to take place at about this time in history. For we like to think of the “atomic age” as one in which things are happening fast, and we must therefore take stock often.

Not too many years ago, the bulk of medical research was relatively poorly financed, and was not at all self-conscious; being, in the main, an avocation of the advanced teacher. Such were the days when it could be said that more money was spent in a football game than in a year’s cancer research. Basic and applied science were then clearly marked apart, by motives, techniques, and financing.

All this has changed. Science is now in the big money; the borderland between basic and applied science has become obscure, and it often seems that the purity of a scientific endeavor is a function of the investigator rather than of the problem. The output has gone up, but the output per capita has mysteriously gone down. The old-timer finds this situation at once exciting and disquieting, especially as he sees that things have still not reached an equilibrium state, and is not quite sure what that will be.

Against this backdrop, we have the prodigious developments in atomic energy which grew out of a few facts discovered just before the war. These, and certain other developments occurring in the same period, make it appear that a massive effort, enormously financed, can untangle a major problem in record time; that “pure” scientists can participate successfully, in fact are indispensable, in such an endeavor; that compartmentalization and secrecy did not prevent it; and that scientific developments are essential to the security of a nation in a troubled world.

Out of this has grown an attitude whose results trend, severally towards good and evil. On the good side of the ledger, we see better financing of research, and more recognition of the importance of the scientist—even of the curious, painstaking but erratic, basic researcher—in the community.

Now money is not a bad thing in itself, any more than a root is a tree. But some care and foresight are necessary, and most of us have not had experience in this sort of tree surgery. Expensive apparatus and materials are required for many of the things we want to do, and a larger research team helps up to the point where its talent becomes subordinate to its direction.

People tend, however, to look upon money as something which buys a tangible commodity. With the additional money that is being thrown into the pot emanating so largely from sources which feel that they are buying technological advances or national security or better medical care, there is a tendency to siphon relatively more of this into projects or problems (that is, predictable science) than into basic or unpredictable fields. And I may say that under this stimulus, much predictable science masquerades as basic.

The universities are, of course, always striving valiantly to keep science pure. But they are forced more and more to accept the "project" and to absorb into its administrative web those scholars with tutorial and inquisitive talents that can ill be spared. Occasionally—and that is too often—the project attitude sours the milk on which Ph.D.'s are suckled.

Here it may be well to mention a salutary change in attitudes in science and research that has been epitomized in the area of atomic medicine. The old-time mutual suspicion existing between M.D.'s and Ph.D.'s has been greatly alleviated. The two trainings each have much to offer: the doctor of medicine, if his training is what it always should be, learns of necessity a great breadth of background in the biological, physical, and social sciences, and perceives the need for their coordination on the level of humanity; the doctor of philosophy gains his laurels through beating out the brains of a particular problem. It is under the influence of the atomic age that not only have doctors been learning about physics, but physicists about thyroid physiology and embryologists about cancer. At its best, this tendency can lead to a broadening and deepening of two mutually related disciplines, both of which have sometimes showed tendencies to become routine in two totally different ways.

Routineness is, of course, a natural form of resistance against the very bigness of science and medicine. More and more time is spent in keeping open the communications. This trouble arises at the same time as the healthy opening up of new borderlands such as biophysics and the genetics of microbes. The resultant structure of science, basic and applied, can become like a building so tall that most of the floor area is in elevator shafts. Against this, technical means must be devised to ensure dissemination of the new, basic relations which are rarely discovered and not always easily recognized—and students must be taught to recognize them. For teaching is an art, and unlike administration, an art longer than life, and one that can undergo irreversible deterioration.

Compartmentalization and secrecy have had their share of public debate. Both lead to an inbreeding of thought and viewpoint, and should be used with

the utmost caution. At the present time, and I believe as a result of the debate, they are being used wisely and conservatively. If we are faced with a long crisis, however, we must remember that much of human progress is attributable to communication and freedom of inquiry. Secrecy is like a heroic remedy prescribed for a patient facing impending doom.

The apotheosis of compartmentalization is seen in the attitude of the Soviet government to theory in science and, in current particular, in genetics. Here, only one compartment is permitted. If anyone has been worried about the loyalty to our system of the erratic, disturbingly objective scientist, let him note well the almost ruthless indignation of our entire scientific community over the banishing of intellectual freedom for its inconvenience to a government. I doubt if any other aspect of democracy has been so stoutly defended by any other definable group.

"Michurin's materialist trend in biology," says Pravda, "is the only scientific one because it is based on dialectic materialism—the revolutionary transformation of the world in the interests of the people. . . . The struggle of Michurin's followers with those of Weissmann is a form of the class ideological struggle of Socialism against capitalism on the international arena, and against the remnants of bourgeois ideology among a section of scientists inside our own country." This may sound funny, yet it annoys us. Let us avoid confusing ourselves about what makes us indignant—it is not the trend of Michurin and Lysenko that is wicked or necessarily wrong; it is the attitude that their unproven views must be right because somebody with influence likes them.

There still exists the possibility that such a self-defeating trend could happen here, now that politics is aware of basic science as something to be afraid of. Anti-intellectual trends are not new to society; but fear of the power of the mind shows signs of becoming crystallized as a result of some of the things we are speaking of. If freedom of movement of scientists must be controlled now, this may be rational; but what freedom may next be lost? Let us just keep in mind that scientific objectivity is one of the most easily defined criteria of democracy and that its rejection by Comrade Stalin and by Hitler in his race theories is the antithesis of what we stand for and what, in the long run, we may rely on for survival of our system. For this muddled "materialism" must eventually lead to a withering away of material progress where it is practiced.

May I say, finally, that the medical man stands squarely between science and society; dealing with the intellectual issue of basic science as a source of his special ability, and dealing personally in his service with man of all sorts and beliefs. In these capacities he can do much to keep our democracy stable and to preserve the purity of science.

AN INTEGRATION

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While your attention is still in its most benevolent stage, I would like to present the leitmotiv of what I have to say. In a word, it is interaction: the interaction of theory with practice, of experience with ideas, of noumenon with phenomenon, of all that mankind at any time has found empirically valuable in the healing arts or sciences with all the ideas, concepts, assumptions, formulations, and theories that have in turn been derived from man's almost divine propensity to reflect upon experience.

For the potentialities of the future owe their sure variety and their certain abundance not only to the cumulative and convergent discoveries of the past, but also to the wholly remarkable ability of the human mind to formulate new concepts from experiments engendered even by outworn creeds or assumptions later proven only partly true. Viewed as a kind of perpetual renewal or refreshed continuum, this principle of interaction finds its biological analogue not in the fission of microorganisms but in perpetuation through sexual reproduction: experience mating with reflection, and vice versa, to produce new forms of experience as well as novel theories, each in turn ready in their maturity to produce another generation, in a continuing line.

So helpful to the comprehensive view of any large class of phenomena is this principle of interaction that I feel almost fettered by the inadequacies of the English language to express interaction. Verbs, we are told by the grammarians, are words of action, and they are transitive or intransitive, and in the active, passive, or reflexive form. What an enormous gain we could enjoy if verbs in English had a special form to indicate forms of action that start a state of interaction—when the object of the verb reacts on the subject. Instead of saying that one hundred years ago some extraordinarily wise, foresighted, and unselfish men created the Mount Sinai Hospital, we should have a form of the word “created” that would assert quite explicitly that they created and were in turn created by the Mount Sinai Hospital. What a vivid and accurate device to express situations so often beclouded by the mere transitive form of the verb! Imagine the advantage of being able to declare in a single word not only that Mr. Smith married Miss Jones, but that a continuing state of interaction was thereby instituted, in which Miss Jones just as certainly married Mr. Smith—in a very transitive sort of way. Or, one could have the neat opportunity of stating not merely that Mr. Brown came to hate Mr. Higginbotham but that Mr. Brown thereby began an emotional relationship with Mr. Higginbotham that was mutual, reciprocal, interacting, hearty, and continuing.

If you have understood my attempt to emphasize this principle of interaction, you have the passkey to four large rooms we can explore, not only now but at your later lesiure. These rooms contain much, but by no means all, of what the preceding speakers have presented to you. My task, being one of integration,

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concerns the arrangement and exposition of facts and forces and their interrelations, rather than mere headlines of their existence or measurements of their separate strengths. Though a remarkably large and variant series of events and opinions can be strung like beads upon the thread of narrative and time sequence, I sensibly left to Dr. Shryock the problem of presenting you with the historical perspectives appropriate to the centenary celebration of a leading American hospital.

As maps of the world use longitude and latitude, or as maps of smaller areas employ the two-dimensional framework of the points of the compass, I propose to present the world of medicine in this wise: in the place of North, I will put man as an organism, and at the South, man's idea of himself. Into this antithesis of empirical fact with conceptual theory enters the factor of interaction, of the interplay of opposites, the reciprocal effects that I have already described. Then, at right angles to the axis of man and his ideas of himself, in the East I'll put man's environment, and in the West man's ideas regarding his environment.

In such a frame of reference many of the events and forces in the world of medicine can be in some measure placed, but if some of you instantly find this scheme too flat and static, let me say that when I've finished with this map, I propose to add a more dynamic element that will supply the freedom of the third dimension. This you will see later: I will not risk confusion by further reference to it now.

What follows, in accordance with my map, will refer to four different areas or regions of medicine: the changes medicine is bringing about in man and in man's idea of himself, and then the changes that medicine is bringing about in man's environment and in man's ideas regarding his environment.

When the word "medicine" is used, I shall mean what I would like to call Great Medicine—a deliberately and explicitly inclusive term meaning the art and the science of medicine, the aggregate of all its specialties and subdivisions, its basic sciences, its clinical and its community applications. Having been brought up in Colorado, I knew and used a similarly comprehensive term, the Great Plains—a pair of words that comprised in realistic description the arbitrary, man-made circumscriptions of the Dakotas, Nebraska, Kansas, Oklahoma, and parts of Texas, New Mexico, Colorado, Wyoming, and Montana. Great Medicine as an inclusive term would thus escape confusion with what is meant by Internal Medicine, or with medical specialties as distinguished from surgical specialties, or with the medicine that comes in a bottle or justifies the never-too-sharp hypodermic needle.

And I would add that Great Medicine deserves its name if only because it has produced great changes—great changes both in point of quality and quantity.

First, let us look at the North of our map—man as an organism. Here Great Medicine has brought about a number of considerable changes. In some areas of the world today, human beings are better nourished throughout their lives than—with rare exceptions—they have ever been in the past. And in all areas of the world, human beings could be better nourished. Exact medical knowledge of nutritional needs and of the physiology of nutrition provides a basis for selecting

the healthiest foods. Exact bacteriological knowledge adds to our ability to store and preserve food. Inventions such as farm machinery; the railroads, automobiles, and steamships; and the telephone, telegraph, and radio all contribute facilities of revolutionary power to make our medical knowledge of nutrition more effective. But, regarded biologically, the well-nourished organism, man, has increased in stature, in strength, and in viability, as a result of medical knowledge.

General hygiene has similarly improved the human organism. Few realistic observers of primitive tribes wax lyrical on the subject of the perfection of the hygiene of the aborigine or the usual end results of his ignorance and superstition.

The immunity and resistance of the human organism has been and can be increased by medical measures such as vaccination and immunization, with or without the subject's intellectual understanding of what these measures accomplish. He is made into a resistant organism—a fact that a biologist would not disregard.

Great Medicine has even changed the life span of man as an organism, and changed it so much that an uninformed observer might rationally infer that a group of men with an average life of 68 years belongs, perhaps, to a different species from a group of men who average 40 years of life. Social usage, and even laws like that of primogeniture, that worked well enough when the eldest son inherited at 21 his father's land or business, don't work so well when the old man lives to be 68 and the eldest son has to postpone the responsibilities and opportunities of his heritage until the age of 40 or 45. We all can recognize the social bearing of Julian Huxley's deft observation that man is the only gregarious animal whose social affairs are controlled by individuals who have passed their sexual prime. If man, without the intervention of Great Medicine, is distinguishable from other animals by the much larger fraction of his pre-adult life, then a case can be made for the biological significance of an intervention by Great Medicine that is adding a much longer period of post-adult existence.

Even more far-reaching in its effect in transforming what has been regarded as man, Great Medicine could produce new genetic varieties of man through increasing knowledge and control of human heredity. If we see what selective breeding has done with plants and animals—and I repeat if we *see* (not merely look at) what even our present knowledge of genetics has done with plants and animals—how can we ignore what could be done with man? Let me say that I think that in the field of human heredity opens the most hopeful and reassuring vista I can see for the human race. With the evidence that mutation rates are affected by various forms of radiant energy, the general field of genetics suggests that by the year 2052 Great Medicine may have begun to affect the kinds of human beings then extant—and profoundly. And this reflection leads to one more aspect of the effect of Great Medicine on man as an organism—the population problem.

In India, the human race is producing four and a half million more babies per year than what would maintain the already crowded population. In our country, the rate of reproduction exceeds the rate in India. Have we nothing to learn from India? In matters of population control, the time to start is day before yesterday.

Nor is the population problem simply a quantitative one. Before Great Medicine improved the dubious life expectancy of a baby, it was those who survived that made up the future population; now it is more nearly those who get born. Delicate and thorny as the fact undoubtedly is, the population problem is qualitative as well as quantitative. But in any event, one of the most profound issues that confronts Great Medicine centers around human reproduction. This we shall begin to talk about when it is already late.

So much for the actual effects of medicine on man as an organism and a species. They are already profound and likely to become more so.

Now let us turn to the effects of Great Medicine on man's idea of himself, for imagination acts on future experience as surely as experience fuels the furnace of the reflective mind. Though I am fully aware that I am making a highly selective choice from a huge array of changes in man's ideas of himself, I would suggest three areas that concern us as persons interested in the perspectives of Great Medicine. These are the concept of health, the concept of psychology, and the concept of research. In each case, experience has become conceptualized, put into abstract terms, and formulated clearly enough to create not only more forms of experience immediately but further concepts, theories, and formulations later to be tested.

Empirically, health has been recognized for centuries as something observable, factual, and real. But it was likely to be defined in terms of the absence of disease, just as wholeness, or completeness, or integrity evades definition and asserts its positiveness behind the mask of a double negative. The notoriously circular tendency of definitions shows clearly enough in the double negative involved in the statement that health is the absence of illness. Though we could agree upon no exact date from which to reckon a century of progress, I would be rather inclined to think that the medical concept of health has not been clearly enunciated and widely exchanged for much more than a century. As birds can operate in the air without presumably being able to theorize about air, as fishes swim in water without, I suppose, formulating its definition, and as flying fish by their conduct indicate their familiarity with both media, so man and medical men have experienced health a long time before the advent of physiology, hygiene, or any systematic, exact knowledge of the component factors of health. Even today any fourth-year medical student can quickly name more signs and symptoms of certain disease than equally definite and dependable proofs of health.

In the absence of exact, ordered, sequential knowledge regarding health, the human mind has tended to attribute health to good luck. Indeed, the greatest obstacle to the further advance of preventive medicine lies in the assumption underlying the remark, "Luckily, I have enjoyed good health," as though the expenditure of money and the use of somebody's intellect had not been for most of us at one time or another the price of keeping healthy and, indeed, alive. It is high time that luck moved out of man's idea of good health. It is time for us all to realize that medical foresight and medical care are on a par with food, clothing, and housing as the chief means of staying alive. That is one view that man begins to take of himself that will prove immensely significant in the next hundred years.

Psychology as we understand the word today has not as long a history as the Mount Sinai Hospital. Pre-eminent as an example of a change in man's ideas about himself, psychology seems to me to play to psychiatry somewhat the same role that physiology plays to clinical medicine. Far from admitting the sarcastic view that one has to be a psychologist to see much in psychology, I would hold that the solid advances of psychology, even of the past half century, constitute one of the clearest and most impressive examples of change in man's ideas about man, and one of the pivotal changes in the history of human thought. The emotional life of man has been analyzed and opened for further analysis with unparalleled objectivity. Conceptual formulations are now available that seem to me to have immense meaning for the oncoming years. Not only psychiatry, but medicine as a whole, and, through Ames' work in the field of perception, perhaps the whole field of epistemology, will grow and change as a result of the furtherance of psychology—a change not of man as an organism, but of man's idea of man and his potentialities.

What the concepts of psychology have brought us in comprehending our emotions finds an equal if not, indeed, a more remarkable analogue in a concept now prominent in man's rational existence. I refer to the concept of research—again, a change in man's view of himself and his powers. Obviously, this is a development of much longer history, though its immense acceleration in Great Medicine within the lifetime of the Mount Sinai Hospital gives research something of the character of a newcomer. The faith of the scientist in the scientific method is what I like to think of when I wonder what faith is. And certainly the hope I entertain for what research will bring to Great Medicine amounts to the quintessence of my hopes. For the discovery of the research method has been the discovery of the way to discovery.

As a method, research may address itself to phenomena in medicine that range from molecules, to cells, to organs, to organisms, and to societies. Just as man himself occupies apparently a midway position in size between the extremes of natural objects—atoms and stars—that he can observe in one way or another, so research in medicine, easiest now perhaps when applied to organs, can move in either direction, from organs to the molecular or to the societal extremes—and still be within the rich realm of Great Medicine.

Now let us look at the other dimension of our map—the environment—with its two contrasting poles, the actual environment and man's ideas about his environment.

Great Medicine has changed and is changing the actual environment in which man lives. To many other technologies, especially physics, chemistry, and engineering, medicine owes an immeasurable obligation for help in reaching the objectives medicine has defined. Witness the provision of abundant and safe water, water-borne waste disposal, the control of air pollution, the reduction of disease-bearing flies and other insects such as mosquitoes and lice, and the improvement of vigor and usefulness of domestic animals as sources of food and pleasure. Conspicuous among changes in the environment of man that have resulted from Great Medicine is the growth of cities and the improvement of hygienic housing.

To repeat Dr. Scheele's quotation from Shattuck in 1850, man now has "the same sanitary enjoyments he would have had as an isolated individual." We are even already at the point of controlling the unhealthy extremes of climate through air conditioning. I might at this point record the hope that our schools of tropical medicine will turn attention to the physiological problems of heat loss and stop being parasitized by parasitology. For in point of exact knowledge, man's opportunity to make full use of the solar energy of the tropics depends now more upon advance in his knowledge of physiology than on elaborations of the facts regarding tropical parasites.

One further change in man's environment that Great Medicine has brought—the isolation and protection afforded by the hospital, his environment in illness. In mental disease, the asylum brought protection from his fearful fellow men—still fearful, and bewildered by fear. In infectious disease, the hospital protects his fellow men from his infection. As a change in man's environment when he is least able to protect himself, the hospital is an elegant environmental improvement.

Having all too briefly outlined the effects of Great Medicine on man as an organism and on his changing environment and then the effect of Great Medicine on man's ideas or concepts about himself, let us turn to the changes in man's ideas of his environment. Quite appropriately, near Thanksgiving Day I read Dr. Brues' statement, "When there is wisdom in the handling of problems, concepts follow." I gratefully repeat that statement as an introduction to the concepts man has formulated regarding his environment.

Perhaps the tendency to explain change as due to something that has been *added* has always been a simpler mental operation than to think that change is due to something that has been subtracted or removed. In any event, the long history of man provides us with plenty of reasons to assume that primitive man regarded disease as something coming from the outside. Places, houses, water, food, and even air—an interpretation surviving in the word *malaria*—were considered the sources of disease. Particularly spirits, and gods in a vengeful or malign temper, were held to be the unseen but unchallenged causes of disease. Not until the Greeks advanced the concept that a sickness might be considered as an absence of the natural harmony of the organism was man's observable or imagined environment exonerated from suspicion as the cause of woe. Indeed, I have often thought that Casimir Funk and his concept of vitamins exerted an almost new and, after 30 years of emphasis upon microbial invasion as the cause of disease, a timely corrective in maintaining that some diseases might be due to the absence of something good rather than the presence of something bad. Certainly the earlier history of man's thinking about his environment not only peopled it with spirits but posited calamity as coming from the outside either inexplicably or as retribution for sin. On this last point—sin—all but the psychiatrists among us probably underestimate the role of guilt in derailing human reason: it is formidable. Indeed, I would be almost ready to assert that guilt feelings have had more to do with maintaining man's belief in the animistic and external origin of disease than anything else. I certainly remember clearly my inability as an intern to convince a New Hampshire woman that her giving in

to a guilty passion for mince pie was not the sufficient cause of a cervical carcinoma. And even today the short sentence, "I think I must have eaten something," packs plausibility into one of the most remarkable understatements in the English language.

The importance of man's environment finds modern formulation—and a helpful and rational one—in such words as "geomedicine" and "climatology." Much remains to be done, I suspect, in further analyses and concept-making regarding the environment, whether in terms of physics—temperature, humidity, barometric pressure, and the like—or in terms of radiation, or in terms of chemistry. The remarkable advances in connection with the importance of fluorine in the growth and maintenance of sound teeth illustrate the value of studies that originated in formulating hypotheses from discriminating observation of the environment and then proving them by exact experiment.

As a concept regarding the environment, I suggest with some measure of uncertainty that chance, as it is commonly understood by most people, has unfortunately come to be regarded as playing a role just as irrational, non-material, fatalistic, out of sight, and out of control as an evil spirit. As Dr. Scheele has said, statistical methods came into medicine as the direct result of studying the incidence of disease and death in large numbers of people. But the reason I venture to bracket man's concept of chance with his interpretation of his environment is that both views have absolved him from the exercise of either his mind or his purse. When Herman Biggs insisted that "Health is purchasable," he challenged the passive assumption that morbidity and mortality were matters of chance. The obvious fatalism of the layman about the operation of the laws of chance is matched by his ignorance. As an example: what do you think the chances are that in a group of 20 people there will be a pair that shares the same day and month as their birthday? It is better than a fifty-fifty chance! Our "common sense" on chance cannot always be relied upon, and it is high time that we exercise Lady Luck as the spirit controlling the visitations of disease. If the facts could be rigorously established and mathematically analyzed, most of us here today would be shown to be more in debt to the expenditure of money, our own and others', and the use of brains, our own and others', than to the fickle favors of luck.

Perhaps the most significant change of all that Great Medicine is bringing in man's interpretation or conceptualization of his environment is simply this: we are coming to see that man's most important environment is man. The title of this symposium illustrates this idea: "Medicine and Society." Again I turn to the idea of reciprocal interaction: Great Medicine reinforces and is reinforced by the concept that the most important environment of man is man. The two disciplines in Great Medicine that could, and in some measure already do, infuse and inform all the rest of medicine are psychiatry and preventive medicine. They live and move and have their being in the deepest and widest conviction of man's social nature. Nor has a single speaker yesterday or today ignored, or, indeed, even failed to emphasize human relationships in the teaching, research, and practice of medicine.

Nor can we leave our concept of the environment without a reference to the

approach in the study of living creatures that is known as ecology. In the view of the Scottish ecologist, Fraser Darling, whose book *A Herd of Red Deer* I commend to you as an example of this new kind of study, ecology is better understood as an approach or attitude than as a discipline. Ecology, furthermore, serves as a pleasant introduction to a still more broadly philosophical point of view advanced by Jan Smuts under the name of holism. . . which also could profit Great Medicine whenever the doctor's reach may become as important as his grasp.

In the all but breathless speed with which, in these decades of technological advance, our environment is changing, I would be on guard lest we become cravenly overzealous in our efforts to adapt to change. You will recall the definition of a zealot as one who redoubles his efforts when he has lost sight of his aim. Now, in a traditional culture, the older people are fortified by the strength of tradition, as one can see in India today. In an *adaptive* society, the older people are not fortified by the incessant flood of change. They are annoyed, skeptical, cowed, and even dismayed by it. They become so preoccupied by the task of adjusting to a changing environment that they are likely to think that their failures to adjust are personal, peculiar, and all but sinful. To such lonely sufferers I would offer a consoling doctrine, which, like all doctrines, must have a name. I'd call it Naturalism. Briefly stated—for in an attempt to integrate the other speakers' ideas on medicine and society, I have scant excuse for elaborating an idea of my own—briefly stated, Naturalism assumes that man's normal, smoothly-working soma and psyche represent selective, successful evolution over hundreds of thousands of years in an environment far more simple than the environment man has produced for himself of late. We are changing the environment that, racially, we have learned to survive in. For most of his evolutionary existence man had rougher food, larger in amount for its nutritive value, and so more likely to supply trace elements; more muscular work; more loss of heat; longer hours of sleep; more play; more fear and aggression; less anxiety and self-discipline; and fewer but more intimate human relationships. And when today we want a feeling of well-being, we go on a camping trip and throw ourselves into conditions the race has learned so well how to cope with—plenty of muscular exercise, bare bodies, loss of heat, more sleep, more fooling around, more danger and struggling, less anxiety, and fewer people—and we feel just fine. Well, those are the very conditions the human race has learned how to succeed in. Such vacations are just like asking for an examination in a course the human race has "got down cold" in an experience at least a thousand and perhaps ten thousand times as long as the interval we celebrate today. After playing under one set of rules for 999,900 years and changing them radically in the last 100 years, we just can't take perfect adaptation for granted. I am too Scotch to buy a bill of goods marked "Progress" without reading the fine print. That is the essence of Naturalism. It can be applied to having children, to raising children, to industry, to the professions, to social life, to the situations when it is reasonable not to use reason, to play as well as work, and to other really important issues of living.

So much for the flat, two-dimensional plotting-out of man and his environment

and the interacting effects of man's ideas of himself and of his environment—and the interrelations of these four with Great Medicine.

Now I want to add a third dimension to this attempt at integration, and, as always when a new dimension is added, it seems at first as different and unfamiliar as flying seems to a snail.

Let me start with the contrasted definitions of strategy and tactics. Strategy is the art of knowing when and on what you will engage your strength: in other words, what you will decide is worth doing. Tactics begins after strategy has chosen what you will engage your strength upon. Tactics concerns itself with the economy, speed, deftness, and grace with which you attain the ends chosen by strategy. Now, let us examine Great Medicine in the light of these definitions of strategy and tactics.

The strategy of Great Medicine concerns two different but inescapably connected things, exact knowledge and mutual aid. Exact knowledge supplies to medicine what the logicians call the necessary cause; the principle of mutual aid provides what the logicians call the sufficient cause. You can't start without the necessary cause; you can't arrive without the sufficient cause. When any branch of medicine mastered the etiology of a disease, progress became possible. But applying such knowledge to the advantage of others—what Kropotkin first called the principle of mutual aid—made progress a reality.

Why have I linked so separate a thing as exact (and therefore, usually, scientific) knowledge with principle of mutual aid—the two as comprising the strategy of Great Medicine? Because it seems to me that there is an inevitable sequence that runs as follows: curiosity leads to research, research to knowledge, knowledge to power, and power to responsibility. Look at the developments in atomic physics for a vivid example of this chain of ineluctable sequences ending in responsibility. And if the connection between responsibility and the principle of mutual aid seems unclear or remote, it will, I hope, become less tenuous before I'm through.

Now, as I said, tactics is defined as the skill, economy, and speed with which you reach the ends set by strategy. In these two days, your speakers have excellently presented a hundred and more of the tactical successes, the continuing and the new tactical problems of Great Medicine: the role of institutions, of teaching, of research, of organization for effective medical care, of public health, of military medicine, of economic welfare, of psychiatry, of the implications for medicine that may come from biology and from the biological applications of nuclear energy, and of the history of medicine in American society. They have dealt not only with the tactics but with the strategy of these different aspects of medicine and society. And I have tried to suggest the intimate interaction between ideas and empiric successes, each supplying the other with support and stimulation. How vacuous is strategy in the continuing absence of tactical success! All of us in this symposium have touched in one way or another on the social responsibility of medicine. And that leads to one final consideration, which may at the outset seem remote.

It seems to me that there is much of value for the immediate and the long future of medicine in reflecting upon the difference between the Roman idea of

morality and the Greek idea of virtue. The Romans considered that a man was moral if he followed the mores of his age, his occupation, and his status in society. The Greeks held a man to be virtuous if his conduct was consistent with his convictions. These might be independent of his age or his station—as was the case with Socrates. Only brief reflection prepares one to realize that in these terms a man can be moral without being virtuous, or virtuous without being moral. But an example may help. Suppose you are on a highway where a speed of 60 miles an hour or over is not only permitted but expected. You will be moral in the Roman sense if you follow the mores of that highway. But suppose you know privately that both your front tires are worn out and that driving at 60 miles would endanger not only your own life but that of others. You will be virtuous if you don't exceed 40, but you won't be moral; and other drivers will honk at you. Of course, the acme of virtue in the light of your conviction would be to get off that road at the first opportunity. But the primary point is clear: it is virtuous in the Greek sense for your conduct to be consistent with your convictions, but it may not be moral.

Now this is a point of singular import to men in any profession. For professional men always are party to information and often to convictions that the laity does not have. In fact, it is near to being a definition of professional behavior to see to it that one's conduct is consistent with one's convictions. In the light of what we doctors know, what are we doing? The great strength of preventive medicine is that in the light of what is now exactly known regarding the etiology of a given disease, the physician, the public health officer, or the hospital that attempts to prevent it is virtuous. The purpose of every speaker at this symposium has been to examine and expose his convictions.

Now, being virtuous is often lonely business. Misunderstanding, antipathy, and even apathy may seem to be for some little time the sole reward of virtue. But I am coming to suspect that a pathognomonic, a characteristic, sign of all ethical processes is that they are slow. The heart may leap up at a moral question where we can follow the mores of our age and profession, but questions involving lonely and tortured virtue at times produce bradycardia—a slow, but at least a repetitive, heartbeat.

And now at the end, to pull my threads together: Great Medicine must be concerned with man and his concepts of himself. Empirical facts and theoretical concepts interact on each other both in point of man's experience and his formulations and theories about himself. The same is true of man's actual environment and the interpretations he places on his environment. Human society is itself man's most important environment, and the most powerful strategy for Great Medicine to follow is the combination of scientific knowledge with the principle of mutual aid. In any event, the power that comes from exact knowledge leads inescapably to responsibility. And the problems of responsibility are most wisely settled by the laymen's encouragement and the doctors' exercise of virtue. Exact knowledge will supply convictions in plenty; the spirit of mutual aid will bring abundant opportunity for conduct to match conviction—and *there* will be found, and yours for the finding, the virtue of Great Medicine.

INDEX TO VOLUME NINETEEN

Numbers 2, 3, 4, 5, & 6

In view of its special character, number 1 of this volume is indexed separately on pages immediately preceding this index.

The (*) preceding the page number indicates an original article; the letters "ab" similarly placed indicate an abstract, while "br" similarly placed indicates book review. Author entries are made only for original articles.

- A**CTION of lysozyme on gastrointestinal mucosa, (K. J. Wang, et al.), ^{ab}440
- Acute coronary insufficiency due to acute hemorrhage: an analysis of one hundred and three cases, (A. M. Master, et al.), ^{ab}615
- coronary insufficiency, pathological and physiological aspects, (H. Horn, et al.), ^{ab}690
- Adelman, Milton H., Perforation of the pyriform sinus, a sequela of endotracheal intubation, *665
- Adenoma, islet cell, of the pancreas with increased insulin excretion of the urine, (Victor Willner and V. A. Weinstein), ^{ab}613
- Administration of research programs in the hospital, (M. R. Steinberg), ^{ab}618
- Adrenalin and nor-adrenalin, color reaction distinguishing between, (B. Kisch), ^{ab}433
- Adrenocorticotropin, cortisone and, treatment of disseminated lupus erythematosus, (G. Baehr and L. J. Soffer), ^{ab}440
- effect of cortisone and, therapy on serum proteins in disseminated lupus erythematosus, (Miriam Reiner), ^{ab}693
- Aerosol streptomycin treatment of advanced pulmonary tuberculosis in children, (J. B. Miller, et al.), ^{ab}697
- Aerosols III, an inspiration time meter for quantitative measurement of the inhalation period of mists, (H. A. Abramson, et al.), ^{ab}614
- Aged, fractures of the vertebrae in the, (E. M. Bick), ^{ab}440
- the general hospital in community planning for the, (Martin R. Steinberg), ^{ab}694
- Alkaline phosphatase in experimental biliary cirrhosis, (M. Wachstein and F. G. Zak), ^{ab}434
- Allergy, quinidine, (S. Siegal and H. Horn), ^{ab}433
- Alternation in the electrocardiogram of a three and one-half month old infant, (B. Kisch and B. Richman), ^{ab}433
- Amino acids on a color reaction or aromatic amidines, on the effect of, (F. Lieben), ^{ab}534
- Anal stenosis, postoperative, (R. Turell), ^{ab}434
- Angiocardiography, visualization of the coronary circulation during, (Alvin J. Gordon, et al.), ^{ab}430
- Angiogenesis, relation of lymphocytic infiltration of inflammatory origin to, (E. Moscheowitz), ^{ab}438
- Angioneurotic edema and rash due to aureomycin, reaction in a patient with multiple sensitivities, (A. D. Parets), ^{ab}616
- Anson and Mirsky methods for pepsin and trypsin, use of dried bovine hemoglobin powder in the, (D. Orringer, et al.), ^{ab}431
- Anatomic study, the tympanic plexus, (Samuel Rosen), ^{ab}693
- Angina pectoris, hypertension and, congenital dextrocardia with situs inversus complicated by, (A. M. Master, et al.), ^{ab}612
- Anomalies, boundary, and artifacts in electrophoresis, (M. Reiner), ^{ab}617
- Anoxemia tests, the "2-step" exercise and, (A. M. Master), ^{ab}612
- Anoxic effects on the electrocardiogram produced by the "2-step" test, (A. M. Master), ^{ab}615
- Antibiotics, the experimental background and clinical use of, (P. H. Long, et al.), ^{ab}615
- Anticoagulant (dicumarol), use of, in preventing post-irradiation tissue changes in the human lung, preliminary report, (S. H. Macht and H. J. Perlberg), ^{ab}437
- Antihistaminic compounds containing the pyridine radical, a quantitative method for the determination of, (Ely Perlman), ^{ab}531
- Antipruritic, n - ethyl - o - crotono - toluidide (eurax) as an antipruritic, (S. M. Peck and T. Michelfelder), ^{ab}697
- Anuria following radiation therapy in leukemia, (Harold Lear and Gordon D. Oppenheimer), ^{ab}692
- Appraisal of the operation of anterior resection for carcinoma of rectum and rectosigmoid, (John H. Garlock and Leon Ginzburg), ^{ab}533
- Armstrong, George E., Century of military medicine, *754
- Aromatic amidines, on the effect of amino acids on a color reaction or, (F. Lieben), ^{ab}534
- Artefohin and trifidin, therapy of ragweed hay fever with electrophoretically isolated fractions, (H. A. Abramson, et al.), ^{ab}698

- Arteriolar sclerosis, renal, the role of lipid deposition in, (S. L. Wilens and S. K. Elster), ^{ab528}
- Arteriosclerosis and diabetes, *411
hyperplastic, versus atherosclerosis, (Eli Moschowitz), ^{ab692}
- Artery, pulmonary, isolated interventricular septal defect with dilatation of the, (I. G. Kroop and A. Grishman), ^{ab691}
pulmonary, technic for measuring cardiac output directly by cannulation of the, (R. D. Seely and D. E. Gregg), ^{ab433}
- Artifacts in electrophoresis, boundary anomalies and, (M. Reiner), ^{ab617}
- Atherosclerosis, hyperplastic arteriosclerosis versus, (Eli Moschowitz), ^{ab692}
- Atomic age, implications in the, medicine and society, *812
- Atresia, congenital, of pulmonary and tricuspid valves, (S. K. Elster), ^{ab529}
congenital tricuspid, the variability of the electrocardiogram in, (I. G. Kroop and A. Grishman), ^{ab695}
- Aureomycin, angioneurotic edema and rash due to, reaction in a patient with multiple sensitivities, (A. D. Parets), ^{ab616}
concentration of the blood, a rapid method for the determination of the, (S. S. Schneierson), ^{ab613}
in blood and urine, fluorophotometric estimation of, (A. Saltzman), ^{ab431}
in the treatment of experimental and clinical infections with H. influenzae, type B, (C. A. Chandler and H. L. Hodes), ^{ab432}
sensitivity reactions to, (S. M. Peck and F. F. Feldman), ^{ab530}
- Auricular fibrillation, early observations on the mechanism of, (B. S. Oppenheimer and Adele O. Friedman), ^{ab697}
- B**ACITRACIN levels in the cerebrospinal fluid after parenteral injections, bacitracin therapy of experimental staphylococcal meningitis in the dog, (P. Teng and F. L. Meloney), ^{ab439}
- Baehr, George, Medicine and the community: the role of the voluntary hospital in community medical care, *744
- Bakst, Alvin A., Myoma of the second portion of duodenum, case report, *677
- Basic amines in the blood under physiologic and pathologic conditions, some studies on, (Kurt Elias and Herbert Elias), ^{ab614}
- Biatritium, cor, triloculare, (Benjamin Riehmman), ^{ab617}
- Bick, Edgar M., The osteohistology of the normal human vertebra, its relation to scoliosis and certain lesions incident to growth and senescence, *490
- Biliary cirrhosis, alkaline phosphatase in experimental, (M. Wachstein and F. G. Zak), ^{ab434}
tract obstruction, spontaneous rupture of normal gall bladder due to, *428
- Biological foundations, medicine and society, *716
- Biopsy, sigmoidoscopy and, (R. Turell and B. J. Garson), ^{ab432}
- Blood and urine, fluorophotometric estimation of aureomycin in blood and urine, (A. Saltzman), ^{ab431}
aureomycin concentration of the, a rapid method for the determination of the, (S. Schneierson), ^{ab613}
coagulation, recent advances in the theory of, *619
flow, digital, observations on the calorimetric method for measuring, (M. Mendlowitz), ^{ab616}
flow measured calorimetrically, quantitative, in the human toe in normal subjects and in patients with residua of trench foot and frostbite, (Milton Mendlowitz and Harold A. Abel), ^{ab431}
of albino rats, disappearance of hyaluronidase from the, (S. K. Elster and E. L. Lowry), ^{ab528}
the normal, pressure range and its clinical implications, (A. M. Master, et al.), ^{ab697}
under physiologic and pathologic conditions, some studies on basic amines in the, (Kurt Elias and Herbert Elias), ^{ab614}
vessel bank under military conditions, (Elliott S. Hurwitt), ^{ab431}
- Boas, Ernst P., Arteriosclerosis and diabetes, *411
- Boundary anomalies and artifacts in electrophoresis, (M. Reiner), ^{ab617}
- Bovine hemoglobin powder, use of dried, in the Anson and Mirsky methods for pepsin and trypsin, (D. Orringer, et al.), ^{ab431}
- Bowel, large, multiple carcinomas of the, (R. H. Marshak), ^{ab535}
- Brodsky, Ralph Howard, Trifacial (trigeminal) neuralgia with emphasis on atypical forms, *596
- Bronchial involvement, sarcoidosis with, a report of two cases with bronchoscopic biopsies, *473
- Brues, Austin M., Medicine and society: implications in the atomic age, *812
- Butanediol-1,3, derivatives of, (G. G. Mayer and H. Sobotka), ^{ab692}
- C**ALORIMETRIC method for measuring digital blood flow, observations on the, (M. Mendlowitz), ^{ab616}
- Cancer, early, of the colon and rectum, the diagnosis of, (E. Granet), ^{ab436}
- Cannulation of the pulmonary artery, technic for measuring cardiac output directly by, (R. D. Seely and D. E. Gregg), ^{ab433}
- Capillary wall, effect of vitamin C deficiency on the diffusion of T-1824 across the, (S. K. Elster and J. A. Schack), ^{ab534}

- Carcinoma, multiple, of the large bowel, (R. H. Marshak), ^{ab}535
- of rectum and rectosigmoid, an appraisal of the operation of anterior resection for, (John H. Garlock and Leon Ginzburg), ^{ab}533
- Cardiac arrhythmia in dextrocardia, (B. Richman), ^{ab}531
- enlargement in nondisabling rheumatic valvulitis, incidence of, (Arnold L. Bachman), ^{ab}434
- output determined by the Fick procedure and a direct method using the rotameter, a comparison of, (R. D. Seely and D. E. Gregg), ^{ab}433
- reflex, inhibition in the ganoid acipenser sturio, (B. Kisch), ^{ab}437
- Cardiology, electron microscopy as applied to, *606
- Carotid canal as a pathway for extension of infection in the temporal bone, (J. G. Druss), ^{ab}435
- Case of diagnosis (pemphigus)? (S. M. Peck), ^{ab}697
- Cavités d'inlay, considérations générales sur les préparations de, du point de vue bio-fonctionnel, (General considerations on inlay cavity preparation from a biofunctional point of view), (E. Baden), ^{ab}532
- Celiac disease, diagnosis and treatment of, report of 603 cases, (S. V. Haas and M. P. Hass), ^{ab}529
- Cerebrospinal fluid after parenteral injections, bacitracin levels in the, bacitracin therapy of experimental staphylococcal meningitis in the dog, (P. Teng and F. L. Meleney), ^{ab}439
- Cesarean section, recent trends in, (R. G. Douglas and R. Landesman), ^{ab}430
- Chest, roentgenograms of the, (S. L. Halpern), ^{ab}436
- Chloride and inulin spaces, a comparison of the, the extracellular compartment, *653
- Chordae tendineae of the mitral valve, sclerosis of the, (L. Sokoloff, et al.), ^{ab}529
- Chordoma, cranial, (J. Freeman), ^{ab}432
- Cirrhosis, biliary, alkaline phosphatase in experimental, (M. Wachstein and F. G. Zak), ^{ab}434
- Clostridium welchii, from, to the coxsackie viruses: changing microbiology, the William Henry Welch Lecture, *396
- Coagulation, blood, recent advances in the theory of the mechanism of, *619
- Colon and rectum, diagnosis of early cancer of the, (E. Granet), ^{ab}435
- Color reaction distinguishing between adrenalin and nor-adrenalin, (B. Kisch), ^{ab}433
- Colostomy bag, disposable ileostomy and, (Arthur A. Gladstone and Robert Turell), ^{ab}690
- Comb growth in the cockerel, the mechanism of estrogen inhibition of, with histologic observations, (N. F. Boas and A. W. Ludwig), ^{ab}435
- Community medical care, the role of the voluntary hospital in, medicine and the community, *744
- Comparison of eardiae output determined by the Fick procedure and a direct method using the rotameter, (R. D. Seely, et al.), ^{ab}617
- of electrokymography and roentgenkymography in the study of myocardial infarction, (S. Dack, et al.), ^{ab}442
- Congenital atresia of pulmonary and tricuspid valves, (S. K. Elster), ^{ab}529
- dextrocardia with situs inversus complicated by hypertension and angina pectoris, (A. M. Master, et al.), ^{ab}612
- Considérations générales sur les préparations de cavités d'inlay du point de vue bio-fonctionnel, (General considerations on inlay cavity preparation from a bio-functional point of view), (E. Baden), ^{ab}532
- Cor biatriatum triloculare, (B. Richman), ^{ab}617
- Corneal sections, pathology of removed, (J. Laval), ^{ab}437
- Coronary circulation during angiocardiology, visualization of the, (Alvin J. Gordon, et al.), ^{ab}430
- insufficiency, a test for, the two-step exercise electrocardiogram, (A. M. Master), ^{ab}535
- insufficiency, acute, due to acute hemorrhage: an analysis of one hundred and three cases, (A. M. Master, et al.), ^{ab}615
- insufficiency, acute, pathological and physiological aspects, (H. Horn, et al.), ^{ab}690
- Correlation of dental abnormalities in hypopituitarism, *668
- of insulin test studies and clinical results in a series of peptic ulcer cases treated by vagotomy, (V. Weinstein, et al.), ^{ab}434
- Cortisone and adrenocorticotropin therapy on serum proteins in disseminated lupus erythematosus, effect of, (Miriam Reiner), ^{ab}693
- and adrenocorticotropin, treatment of disseminated lupus erythematosus with, (G. Baehr and L. J. Soffer), ^{ab}440
- Coxsackie viruses, from clostridium welchii to the, changing microbiology, the William Henry Welch lecture, *396
- Cranial chordoma, (J. Freeman), ^{ab}432
- Cranin, Norman A., see Brodsky, Ralph Howard, *596
- DALLDORF, Gilbert, The William Henry Welch lecture: from clostridium welchii to the coxsackie viruses: changing microbiology, *396

- Davidoff, Leo M., *Judicium difficile*, a lesson in perspective, *420
- Dental abnormalities in hypo-pituitarism, correlation of, *668
- Derivatives of butanediol-1,3. (G. G. Mayer and H. Sobotka), ^{ab}692
- Dermatologic therapy, diiodohydroxyquinoline in, (William Leifer and Karl Steiner), ^{ab}692
- Determining factors in composing and analyzing speech-hearing tests, (Willis C. Beasley and Harry Rosenwasser), ^{ab}689
- Dextrocardia, cardiac arrhythmia in, (B. Richman), ^{ab}531
- congenital, with situs inversus complicated by hypertension and angina pectoris, (A. M. Master, et al.), ^{ab}612
- Diabetes, arteriosclerosis and, *411
- mellitus, a summary of experimental evidence relating life stress to, *537
- mellitus, the effects of vitamin E administration upon, (H. Pollack, et al.), ^{ab}616
- Diagnosis and treatment of celiac disease, report of 603 cases, (S. V. Haas and M. P. Hass), ^{ab}529
- of early cancer of the colon and rectum, (E. Gränet), ^{ab}436
- Diagnostic electroencephalography, (Hans Strauss, et al.), ^{br}536
- Diarrhea, infantile, associated with pseudomonas aeruginosa, observations on a small outbreak of, (A. L. Florman and N. Schifrin), ^{ab}615
- Dibenamine in chronic simple glaucoma, effect of, (S. Bloomfield and H. Haimovici), ^{ab}614
- Dicumarol, major surgery, digitalis and mercurial intoxication, penicillin, the treatment of heart failure, (A. M. Master, et al.), ^{ab}438
- Diiodohydroxyquinoline in dermatologic therapy, (William Leifer and Karl Steiner), ^{ab}692
- Direct reorientation of behavior patterns in deep narcosis (narcoleptia), (R. M. Brickner, et al.), ^{ab}694
- Disappearance of hyaluronidase from the blood of albino rats, (S. K. Elster and E. L. Lowry), ^{ab}528
- Disposable ileostomy and colostomy bag, (Arthur A. Gladstone and Robert Turell), ^{ab}690
- Disseminated lupus erythematosus, effect of cortisone and adrenocorticotropin therapy on serum proteins in, ^{ab}693
- Distal tibial epiphysis, post-traumatic aseptic necrosis of the, (R. S. Siffert and A. M. Arkin), ^{ab}693
- Does modified measles result in lasting immunity? (S. Karelitz), ^{ab}618
- Dried bovine hemoglobin powder, use of, in the Anson and Mirsky methods for pepsin and trypsin, (D. Orringer, et al.), ^{ab}431
- Duodenum, myoma of the second portion of, case report, *677
- Dynamic nature of thermophily, (Mary Belle Allen), ^{ab}528
- E**ARLY changes caused by radiation, the William Henry Welch lecture, *443
- Ears, experimental evaluation of recording to alternate, as an aid in localization, (M. A. Lennox and J. A. Epstein), ^{ab}695
- Economic welfare, health, medicine, and, *734
- Edema, angioneurotic and rash due to aureomycin, reaction in a patient with multiple sensitivities, (A. D. Parets), ^{ab}616
- physiological considerations of, *537
- Effect of amino acids on a color reaction or aromatic amidines, (F. Lieben), ^{ab}534
- of cortisone and adrenocorticotropin therapy on serum proteins in disseminated lupus erythematosus, (Miriam Reiner), ^{ab}693
- of dibenamine in chronic simple glaucoma, (S. Bloomfield and H. Haimovici), ^{ab}614
- of vitamin C deficiency on the diffusion of T-1824 across the capillary wall, (S. K. Elster and J. Schack), ^{ab}534
- Effects of increased pressure upon sarcoma 180, (Alvin M. Arkin and Kanematsu Sugiura), ^{ab}532
- of various modes of administration of pyribenzamine on the histamine wheal and epidermal sensitivity reactions, (S. M. Peck, et al.), ^{ab}438
- of vitamin E administration upon diabetes mellitus, (H. Pollack, et al.), ^{ab}616
- Electrocardiogram, anoxic effects on the, produced by the "2-step" test, (A. M. Master), ^{ab}615
- in congenital tricuspid atresia, the variability of the, (I. G. Kroop and A. Grishman) ^{ab}395
- of a three and one-half month old infant, alternation in the, (B. Kisch and B. Richman), ^{ab}433
- the two-step exercise, a test for coronary insufficiency, (A. M. Master), ^{ab}535
- the "two-step" exercise, in functional heart disturbances and in organic heart disease: the use of ergotamine tartrate, (A. M. Master, et al.), ^{ab}530
- Electroencephalographic findings in measles encephalitis, (H. Hodes and S. Livingston), ^{ab}534
- Electroencephalogram, epilepsy and the, *683
- Electroencephalography, diagnostic, (Hans Strauss, et al.), ^{br}536
- Electrokymographic study, ventricular contraction in Wolff-Parkinson-White syndrome: an, (S. Dack, et al.), ^{ab}442

- Electromyography, localization of cord tumors by, (Sidney M. Cohen), ^{ab}533
- Electron microscopy as applied to cardiology, *606
- Electrophoresis, boundary anomalies and artifacts in, (M. Reiner), ^{ab}617
- Electrophoretic studies on the protein distribution in normal human serum, (M. Reiner), ^{ab}440
- Electrophoretically isolated fractions (artefolin and trifidin), therapy of ragweed hay fever with, preliminary report, (H. A. Abramson, et al.), ^{ab}698
- Emotional stress in relation to attacks of multiple sclerosis, (R. M. Brickner and D. J. Simons), ^{ab}432
- Endometriosis of the large bowel treated with testosterone, (R. H. Marshak and A. I. Friedman), ^{ab}530
- Endotracheal intubation, perforation of the pyriform sinus, a sequela of, *665
- Enzymes, histochemistry of, *446
- Epidermal sensitivity reactions, effects of various modes of administration of pyribenzamine on the histamine wheal and, (S. M. Peck, et al.), ^{ab}438
- Epilepsy and the electroencephalogram, *683
- Ergotamine tartrate, the use of, the "two-step" exercise electrocardiogram in functional heart disturbances and in organic heart disease, (A. M. Master, et al.), ^{ab}530
- Erythrocytes in a case of atypical retinitis pigmentosa, malformation of the, (F. A. Bassen and A. L. Kornzweig), ^{ab}441
- Esophageal varices, further observations on packing of mediastinum for, (John H. Garlock and Max L. Som), ^{ab}442
- varices, packing of mediastinum in the treatment of hematemesis due to, (John H. Garlock and Max L. Som), ^{ab}430
- Estrogen inhibition of comb growth in the cockerel, with histologic observations, mechanism of, (N. F. Boas and A. W. Ludwig), ^{ab}435
- Eugenol, response of gastric mucous barrier in pouch dogs to repeated topical application of, (H. A. Sober, et al.), ^{ab}693
- toxicity of, determination of LD50 on rats, (H. A. Sober), ^{ab}431
- toxicity of the mucigogue, administered by stomach tube to dogs, (F. U. Lauber and F. Hollander), ^{ab}691
- Eurax, n-ethyl-o-crotono-toluide, as an antipruritic, (S. M. Peck and T. Michelfelder), ^{ab}697
- Evaluation of the mumps skin test, (A. L. Florman, et al.), ^{ab}435
- Experimental approaches to psychodynamic problems, *639
- background and clinical use of antibiotics, (P. H. Long, et al.), ^{ab}615
- evaluation of recording to alternate ears as an aid in localization, (M. A. Lennox and J. A. Epstein), ^{ab}695
- Extensor muscles of the wrist, weakness of, an early sign in hemiparesis, (I. Strauss), ^{ab}439
- Extracellular compartment: a comparison of the chloride and inulin spaces, *653
- F**EMORAL artery, successful removal of a tumor embolus from the, (L. Blum), ^{ab}441
- Fick procedure and a direct method using the rotameter, a comparison of cardiac output determined by the, (R. D. Seely, et al.), ^{ab}617
- Fluorophotometric estimation of aureomycin in blood and urine, (A. Saltzman), ^{ab}431
- Folic acid antagonists in human neoplasia, some theoretical and practical aspects of the use of, *583
- Fractures of the vertebrae in the aged, (E. M. Bick), ^{ab}440
- Frostbite, trench foot and, quantitative blood flow measured calorimetrically in the human toe in normal subjects with residua of, (Milton Mendlowitz and Harold A. Abel), ^{ab}431
- Further observations on packing of mediastinum for esophageal varices, (John H. Garlock and Max L. Som), ^{ab}442
- G**ALL bladder, normal, spontaneous rupture of, due to biliary tract obstruction, *428
- Ganoid acipenser sturio, reflex cardiac inhibition in the, (B. Kisch), ^{ab}437
- Gastric mucous barrier in pouch dogs, response of, to repeated topical application of eugenol, (H. A. Sober, et al.), ^{ab}693
- Gastrointestinal mucosa, action of lysozyme on, (K. J. Wang), ^{ab}440
- General hospital in community planning for the aged, (Martin R. Steinberg), ^{ab}694
- Ginzberg, Eli, Health, medicine, and economic welfare, *734
- Glaucoma, chronic simple, effect of dibenamine in, (S. Bloomfield and H. Haimovici), ^{ab}614
- Glioma of the retina in father and child, (J. Laval), ^{ab}691
- Globus, Joseph H., obituary, *iv
- Glycerite of hydrogen peroxide on the human skin, skin reactions XVII, (H. A. Abramson), ^{ab}689
- Gomori, G., Histochemistry of enzymes, *446
- Graft, the ultimate fate of the, (Herbert M. Katzin), ^{ab}437
- Gregg, Alan, An integration, *821
- Greenspan, Ezra M., Some theoretical and practical aspects of the use of folic acid antagonists in human neoplasia, *583
- Greenstein, Louis, Epilepsy and the electroencephalogram, *683

- Gynecological, obstetrical and, aspects of proctology; review of literature with comments, (R. Turell), ^{ab531}
- I**NFLUENZAE, type B, aureomycin in the treatment of experimental and clinical infections with, (C. A. Chandler and H. L. Hodes), ^{ab432}
- Hay fever, ragweed, therapy of, with electrophoretically isolated fractions (arte-folin and trifidin), preliminary report, (H. A. Abramson, et al.), ^{ab698}
- Health, medicine, and economic welfare, ^{*734}
public, 1852-1952, ^{*764}
- Heart disturbances, functional, and in organic heart disease, the "two-step" exercise electrocardiogram in, the use of ergotamine tartrate, (A. M. Master, et al.), ^{ab530}
failure, the treatment of, digitalis and mercurial intoxication, penicillin, dicumarol, major surgery, (A. M. Master, et al.), ^{ab438}
- Hematemesis due to esophageal varices, packing of mediastinum in the treatment of, (John H. Garlock and Max L. Som), ^{ab430}
- Hemiparesis, an early sign of, weakness of the extensor muscles of the wrist, (I. Strauss), ^{ab439}
- Hemorrhage, acute, coronary insufficiency due to, an analysis of one hundred and three cases, (A. M. Master, et al.), ^{ab615}
- Hepatic dysfunction, thrombocytopenic purpura, and isolated peripheral nerve palsy, infectious mononucleosis: with, (R. S. Wallerstein and L. Madison), ^{ab618}
- Hepatis peliosis, (F. G. Zak), ^{ab432}
- Hernia in the aged, surgical treatment of, (Frank P. Sainburg), ^{ab693}
transesenteric, ^{*465}
- Hinkel, Lawrence E., Jr., A summary of experimental evidence relating life stress to diabetes mellitus, ^{*537}
- Hirsh, Joseph, The Jews' hospital and psychological medicine, ^{*481}
- Histamine wheal and epidermal sensitivity reactions, effects of various modes of administration of pyribenzamine on the, (S. M. Peck, et al.), ^{ab438}
- Histochemistry of enzymes, ^{*446}
- Historical perspective, an, medicine and society, ^{*699}
- Hodgkin's disease involving the stomach, (Herbert Sandick), ^{ab612}
disease, simultaneous occurrence of plasma cell multiple myeloma and, (B. B. Greenberg, et al.), ^{ab433}
- Hospital, the general, in community planning for the aged, (Martin R. Steinberg), ^{ab694}
voluntary, in community medical care, the role of the, medicine and the community, ^{*744}
- Hyaluronidase, disappearance of, from the blood of albino rats, (S. K. Elster and E. L. Lowry), ^{ab528}
- 2-Hydroxystillbamidine in urine and tissue, quantitative determination of stilbamidine and, (F. Lieben and I. Snapper), ^{ab534}
- Hypermetabolic states without hyperthyroidism (nonthyrogenous hypermetabolism), (S. Silver, et al.), ^{ab439}
- Hyperplastic arteriosclerosis versus atherosclerosis, (Eli Moschcowitz), ^{ab692}
- Hypertension and angina pectoris, congenital dextrocardia with situs inversus complicated by, (A. M. Master, et al.), ^{ab612}
- Hyperthyroidism, hypermetabolic states without, (nonthyrogenous hypermetabolism), (S. Silver, et al.), ^{ab439}
- Hypopituitarism, correlation of dental abnormalities in, ^{*668}
- Hystero-graphy and hysterosalpinography: analysis of 2,500 cases with special emphasis on technic and safety of the procedure is presented, (R. H. Marshak, et al.), ^{ab696}
- I**DIOPATHIC thrombocytopenic purpura, recent observations on the pathogenetic mechanism of, ^{*452}
- Ileostomy and colostomy bag, disposable, (Arthur A. Gladstone and Robert Turell), ^{ab690}
- Incidence of cardiac enlargement in non-disabling rheumatic valvulitis, (Arnold L. Bachman), ^{ab434}
- Infectious mononucleosis: with hepatic dysfunction, thrombocytopenic purpura, and isolated peripheral nerve palsy, (R. S. Wallerstein and L. Madison), ^{ab618}
- Inhalation period of mists, aerosols III, an inspiration time meter for quantitative measurement of the, (H. A. Abramson, et al.), ^{ab614}
- Inspiration time meter for quantitative measurement of the inhalation period of mists, aerosols III, (H. A. Abramson, et al.), ^{ab614}
- Insulin excretion of the urine, islet cell adenoma of the pancreas with increased, (Victor Willner and V. A. Weinstein), ^{ab613}
test always reliable? is the, (V. Weinstein and F. H. Hollander), ^{ab532}
test studies and clinical results in a series of peptic ulcer cases treated by vagotomy, correlation of, (V. Weinstein, et al.), ^{ab434}
- Intestinal obstruction, chronic, Meckel's diverticulum producing, (R. H. Marshak and A. I. Friedman), ^{ab696}
- Intussusception, peritonscopic, operative cure, Meckel's diverticulum, (M. S. Harte and M. G. Elias), ^{ab436}
- Inulin spaces, a comparison of the chloride and, the extracellular compartment, ^{*653}

- Is the insulin test always reliable? (V. Weinstein and F. H. Hollander), ^{ab532}
- Islet cell adenoma of the pancreas with increased insulin excretion of the urine, (Victor Willner and V. A. Weinstein), ^{ab613}
- Isolated interventricular septal defect with dilatation of the pulmonary artery, (I. G. Kroop and A. Grishman), ^{ab691}
- Isotopes, radioactive, in medicine, uses of, (L. R. Wasserman and B. Loevinger), ^{ab531}
- J**EW'S hospital and psychological medicine, *481
- Judicum difficile, a lesson in perspective, *420
- K**AHN, Alvin J., Spontaneous rupture of normal gall bladder due to biliary tract obstruction, *428
- Kaufman, M. Ralph, see Hirsh, Joseph, *481
- Kisch, Bruno, Electron microscopy as applied to cardiology, *606
- L**EITER, H. Evans, see Osserman, Kermit E., *424
- Lempert, Julius, Otology: its present status, *381
- Leukemia, anuria following radiation therapy in, (Harold Lear and Gordon D. Oppenheimer), ^{ab692}
- Levitt, Marvin F., Physiological considerations of edema, *653
- Liaison psychiatry pays an extra dividend, (M. R. Steinberg), ^{ab618}
- Lipid deposition in renal arteriolar sclerosis, the role of, (S. L. Wilens and S. K. Elster), ^{ab528}
- Lobectomy in a patient eighty-two years of age, (M. B. Rosenblatt, et al.), ^{ab617}
- Localization of cord tumors by electromyography, (Sidney M. Cohen), ^{ab533}
- Lung, human, use of anticoagulant (dicumarol) in preventing post-irradiation tissue changes in the, (S. H. Macht and H. J. Perlberg), ^{ab437}
- lobectomy, mucocellular papillary adenocarcinoma of the, five-year follow-up, (K. E. Osserman and H. Neuhof), ^{ab616}
- Lupus erythematosus, disseminated, treatment of, with cortisone and adrenocorticotropin, (G. Baehr and L. J. Soffer), ^{ab440}
- erythematosus, disseminated, effect of cortisone and adrenocorticotropin therapy on serum proteins in, (Miriam Reiner), ^{ab693}
- Lymphocytic infiltration of inflammatory origin to angiogenesis, relation of, (E. Moscheowitz), ^{ab438}
- Lysozyme on gastrointestinal mucosa, action of, (K. J. Wang, et al.), ^{ab440}
- M**ALFORMATION of the erythrocytes in a case of atypical retinitis pigmentosa, (F. A. Bassen and A. L. Kornzweig), ^{ab441}
- Masserman, Jules H., Experimental approaches to psychodynamic problems, *639
- Measles encephalitis, electroencephalographic findings in, (H. Hodes and S. Livingston), ^{ab534}
- modified, does, result in lasting immunity? (S. Karelitz), ^{ab618}
- Measurement, quantitative, of the inhalation period of mists, aerosols III, an inspiration time meter for, (H. A. Abramson, et al.), ^{ab614}
- Mechanism of estrogen inhibition of comb growth in the cockerel, with histologic observations, (N. F. Boas and A. W. Ludwig), ^{ab435}
- Meckel's diverticulum, intussusception, peritonoscopy, operative cure, (M. S. Harte and M. G. Elias), ^{ab436}
- diverticulum producing chronic intestinal obstruction, (R. H. Marshak and A. I. Friedman), ^{ab696}
- Mediastinum, packing of, for esophageal varices, further observations on, (John H. Garlock and Max L. Som), ^{ab442}
- packing of, in the treatment of hematemesis due to esophageal varices, (John H. Garlock and Max L. Som), ^{ab430}
- Medicine and the community: the role of the voluntary hospital in community medical care, *744
- and society: a century of military medicine, *754
- and society: an historical perspective, *699
- and society: an integration, *821
- and society: implications in the atomic age, *812
- and society: the biological foundations, *716
- and society: the role of psychiatry, *790
- Menninger, William C., Medicine and society, the role of psychiatry, *790
- Mercurial diuresis in elderly persons, the salt depletion syndrome following, (H. L. Jaffe, et al.), ^{ab691}
- intoxication, digitalis and, penicillin, dicumarol, major surgery, the treatment of heart failure, (A. M. Master, et al.), ^{ab438}
- Methods, newer, in the diagnosis of viral diseases, (A. L. Florman), ^{ab435}
- Microbiology, changing, from clostridium welchii to the coxsackie viruses, the William Henry Welch lecture, *396
- Microscopy, electron, as applied to cardiology, *606
- Military conditions, a blood vessel bank under, (Elliott S. Hurwitt), ^{ab431}
- medicine, a century of, *754
- Mitral valve, sclerosis of the chordae tendineae of the, (L. Sokoloff, et al.), ^{ab529}

- Mononucleosis, infectious, with hepatic dysfunction, thrombocytopenic purpura, and isolated peripheral nerve palsy, (R. S. Wallerstein and L. Madison), ^{ab}618
- Mucocellular papillary adenocarcinoma of the lung lobectomy, five-year follow-up, (K. E. Osserman and H. Neuhof), ^{ab}616
- Multiple carcinomas of the large bowel, (R. H. Marshak), ^{ab}535
- myeloma, (I. H. Parnes), ^{ab}433
- myeloma and Hodgkin's disease, simultaneous occurrence of plasma cell, (B. B. Greenberg, et al.), ^{ab}433
- Mycocardial infarction, a comparison of electrokymography and roentgenkymography in the study of, (S. Dack, et al.), ^{ab}442
- Myoma of the second portion of duodenum, case report, *677
- N**-ETHYL-o-crotono-toluide (eurax) as an antipruritic, (S. M. Peck and T. Michelfelder), ^{ab}697
- Narcosis (narcoleptia), direct reorientation of behavior patterns in deep, (R. M. Bruckner, et al.), ^{ab}694
- Necrosis, post-traumatic aseptic, of the distal tibial epiphysis, (R. S. Siffert and A. M. Arkin), ^{ab}693
- Neoplasia, human, use of folic acid antagonists in, some theoretical and practical aspects of the, *583
- Nerve palsy, isolated peripheral, infectious mononucleosis: with hepatic dysfunction, thrombocytopenic purpura, and, (R. S. Wallerstein and L. Madison), ^{ab}618
- Neuralgia, trifacial (trigeminal), with emphasis on atypical forms, *596
- New method of automatic controlled respiration, (M. H. Adelman, et al.), ^{ab}613
- Normal blood pressure range and its clinical implications, (A. M. Master, et al.), ^{ab}697
- O**BITUARY, Joseph H. Globus, *iv
- Observations on a small outbreak of infantile diarrhea associated with pseudomonas aeruginosa, (A. L. Florman and N. Schifrin), ^{ab}615
- Obstetrical and gynecological aspects of proctology; review of literature with comments, (R. Turell), ^{ab}531
- Ossermann, Kermit E., Perinephric and renal cortical abscess due to colon bacillus without bacteriuria or pyuria, *424
- Osteohistology of the normal human vertebra, its relation to scoliosis and certain lesions incident to growth and senescence, *490
- Otology: its present status, *381
- Oxygen heterocycles, synthesis and properties of spiranes containing, (J. D. Chanley), ^{ab}528
- P**ANCREAS, islet cell adenoma of the, with increased insulin excretion of the urine, (Victor Willner and V. A. Weinstein), ^{ab}613
- Pancreatic function, studies in, II—a statistical study of pancreatic secretion following secretin in patients without pancreatic disease, (D. A. Dreiling and F. Hollander), ^{ab}695
- Pathogenetic mechanism of idiopathic thrombocytopenic purpura, recent observations on the, *452
- Pathology of removed corneal sections, (J. Laval), ^{ab}437
- Pediatric proctology, review with comment, (R. Turell), ^{ab}439
- Peliosis hepatis, (F. G. Zak), ^{ab}432
- Penicillin, an unusual sensitivity reaction to, report of a case with autopsy findings, (Robert M. Berne), ^{ab}533
- Pepsin and trypsin, use of dried bovine hemoglobin powder in the Anson and Mirsky methods for, (D. Orringer, et al.), ^{ab}431
- Peptic ulcer cases treated by vagotomy, correlation of insulin test studies and clinical results in a series of, (V. Weinstein, et al.), ^{ab}434
- Perforation of the pyiform sinus, a sequela of endotracheal intubation, *665
- Perinephric and renal cortical abscess due to colon bacillus without bacteriuria or pyuria, *424
- Plasma cell multiple myeloma and Hodgkin's disease, simultaneous occurrence of, (B. B. Greenberg, et al.), ^{ab}433
- Physiological considerations of edema, *571
- Pomeranz, Alfred A., Transmesenteric Hernia, *465
- Post-irradiation tissue changes in the human lung, use of anticoagulant (dicumarol) in preventing, preliminary report, (S. H. Macht and H. J. Perlberg), ^{ab}437
- Postoperative anal stenosis, (R. Turell), ^{ab}434
- Post-traumatic aseptic necrosis of the distal tibial epiphysis, (R. S. Siffert and A. M. Arkin), ^{ab}693
- Proctology, obstetrical and gynecological aspects of, review of literature with comments, (R. Turell), ^{ab}531
- Proctology, pediatric, review with comment, (R. Turell), ^{ab}439
- Proctology, what is new in, (Robert Turell and Albert S. Lyons), ^{ab}613
- Prophylaxis, psychiatric problems of the puerperium from the standpoint of, (L. Linn and P. Polatin), ^{ab}530
- Protein distribution in normal human serum, electrophoretic studies on the, (M. Reiner), ^{ab}440
- Proteins, serum, in disseminated lupus erythematosus, effect of cortisone and adrenocorticotropins on, ^{ab}693

- Pseudomonas aeruginosa*, observations on a small outbreak of infantile diarrhea associated with, (A. L. Florman and N. Schiffrin), ^{ab}615
- Psychiatric problems of the puerperium from the standpoint of prophylaxis, (L. Linn and P. Polatin), ^{ab}530
- Psychiatry, liaison, pays an extra dividend, (M. R. Steinberg), ^{ab}618
- Psychiatry, the role of, medicine and society, *790
- Psychodynamic problems, experimental approaches to, *639
- Psychological medicine, the Jews' hospital and, *481
- Psychosomatic illness, psychotic factors in, (Jesse Appel and Samuel Richard Rosen), ^{ab}689
- Psychotic factors in psychosomatic illness, (Jesse Appel and Samuel Richard Rosen), ^{ab}689
- Public Health, 1852-1952, *764
- Puerperium, psychiatric problems of the, from the standpoint of prophylaxis, (L. Linn and P. Polatin), ^{ab}530
- Pulmonary and tricuspid valves, congenital atresia of, (S. K. Elster), ^{ab}529
- Purpura, idiopathic thrombocytopenic, recent observations on the pathogenetic mechanism of, *452
- Pyribenzamine on the histamine wheel and epidermal sensitivity reactions, effects of various modes of administration of, (S. M. Peck, et al.), ^{ab}438
- Pyridine radical, antihistaminic compounds containing the, a quantitative method for the determination of, (Ely Perlman), ^{ab}531
- Pyriiform sinus, perforation of the, a sequela of endotracheal intubation, *665
- Q**UANTITATIVE blood flow measured calorimetrically in the human toe in normal subjects and in patients with residua of trench foot and frostbite, (Milton Mendlowitz and Harold A. Abel), ^{ab}431
- determination of stilbamidine and 2-hydroxystilbamidine in urine and tissue, (F. Lieben and I. Snapper), ^{ab}534
- method for the determination of antihistaminic compounds containing the pyridine radical, (Ely Perlman), ^{ab}531
- Quinidine allergy, (S. Siegal and H. Horn), ^{ab}433
- R**ADIATION scoliosis: an experimental study, (A. M. Arkin and N. Simon), ^{ab}440
- the early changes caused by, the William Henry Welch lecture, *443
- therapy in leukemia, anuria following, (Harold Lear and Gordon D. Oppenheimer), ^{ab}691
- Radioactive isotopes in medicine, uses of, (L. R. Wasserman and R. Loevinger), ^{ab}531
- Rapid method for the determination of the aureomycin concentration of the blood, (S. S. Schneierson), ^{ab}613
- Recent advances in the theory of the mechanism of blood coagulation, *619
- observations on the pathogenetic mechanism of idiopathic thrombocytopenic purpura, *452
- trends in cesarean section, (R. G. Douglas and R. Landesman), ^{ab}430
- trends in the diagnosis and treatment of varicose veins, (R. S. Nabatoff), ^{ab}616
- Rectum and rectosigmoid, carcinoma, an appraisal of the operation of anterior resection for, (John H. Garlock and Leon Ginzburg), ^{ab}533
- the diagnosis of early cancer of the colon and, (E. Granet), ^{ab}436
- Reflex cardiac inhibition in the *ganoid acipenser sturio*, (B. Kisch), ^{ab}437
- Relation of lymphocytic infiltration of inflammatory origin to angiogenesis, (E. Moschowitz), ^{ab}438
- Renal arteriolar sclerosis, the role of lipid deposition in, (S. L. Wilens and S. K. Elster), ^{ab}528
- cortical abscess, perinephric and, abscess due to colon bacillus without bacteriuria or pyuria, *424
- Research programs in the hospital, administration of, (M. R. Steinberg), ^{ab}618
- Resection, anterior, for carcinoma of rectum and rectosigmoid, an appraisal of the operation of, (John H. Garlock and Leon Ginzburg), ^{ab}533
- Respiration, a new method of automatic controlled, (M. H. Adelman, et al.), ^{ab}613
- Response of gastric mucous barrier in pouch dogs to repeated topical application of eugenol, (H. A. Sober, et al.), ^{ab}693
- Retina, glioma of the, in father and child, (J. Laval), ^{ab}691
- Retinitis pigmentosa, atypical, malformation of the erythrocytes in a case of, (F. A. Bassen and A. L. Kornzweig), ^{ab}441
- Rhinoplasty: surgical complications and how to avoid them, (I. B. Goldman), ^{ab}435
- Roentgenkymography, electrokymography and, in the study of myocardial infarction, a comparison, (S. Dack), ^{ab}442
- Roentgenograms of the chest, (S. L. Halpern), ^{ab}436
- Rheumatic valvulitis, incidence of cardiac enlargement in nondisabling, (Arnold L. Bachman), ^{ab}434
- Role of lipid deposition in renal arteriolar sclerosis, (S. L. Wilens and S. K. Elster), ^{ab}528

- Rotameter, a direct method using the, a comparison of cardiac output determined by the Fick procedure and, (R. Seely, et al.), ^{ab}617
- Rupture, spontaneous, of normal gall bladder due to biliary tract obstruction, *428
- S**ALT depletion syndrome following mercurial diuresis in elderly persons, (H. L. Jaffe, et al.), ^{ab}691
- Salzmann, J. A., Correlation of dental abnormalities in hypo-pituitarism, *668
- Sarcoidosis with bronchial involvement, a report of two cases with bronchoscopic biopsies, *473
- Sarcoma 180, effects of increased pressure upon sarcoma 180, (Alvin M. Arkin and Kanematsu Sugiura), ^{ab}532
- Scheele, Leonard A., Public health, 1852-1952, *764
- Sclerosis of the chordae tendineae of the mitral valve, (L. Sokoloff, et al.), ^{ab}529
- Scoliosis and certain lesions incident to growth and senescence, its relation to, the osteohistology of the normal human vertebra, *490
- radiation, an experimental study, (A. M. Arkin and N. Simon), ^{ab}440
- Secretin in patients without pancreatic disease, a statistical study of pancreatic secretion following, studies in pancreatic function, II, (D. A. Dreiling and F. Hollander), ^{ab}695
- Sensitivity reactions to aureomycin, (S. M. Peck and F. F. Feldman), ^{ab}530
- Septal defect, isolated interventricular, with dilatation of the pulmonary artery, (I. G. Kroop and A. Grishman), ^{ab}691
- Serum, normal human, electrophoretic studies on the protein distribution in, (M. Reiner), ^{ab}440
- Serum proteins in disseminated lupus erythematosus, effect of cortisone and adrenocorticotropin on, ^{ab}693
- Situs inversus complicated by hypertension and angina pectoris, congenital dextrocardia with, (A. M. Master, et al.), ^{ab}612
- Shryock, Richard H., Medicine and society: an historical perspective, *699
- Sigmoidoscopy and biopsy, (R. Turell and B. J. Garson), ^{ab}432
- Siltzbach, Louis E., Sarcoidosis with bronchial involvement, a report of two cases with bronchoscopic biopsies, *473
- Simultaneous occurrence of plasma cell multiple myeloma and Hodgkin's disease, (B. B. Greenberg, et al.), ^{ab}433
- Sjorgen's syndrome, (H. T. Behrman), ^{ab}430
- Skin reactions XVII, the stability of glycerite of hydrogen peroxide on the human skin, (H. A. Abramson), ^{ab}689
- Som, Max L., see Siltzbach, Louis E., *473
- Speech-hearing tests, determining factors in composing and analyzing, (Willis C. Beasley and Harry Rosenwasser), ^{ab}689
- Spiranes containing oxygen heterocycles, synthesis and properties of, (J. D. Chanley), ^{ab}528
- Spontaneous rupture of normal gall bladder due to biliary tract obstruction, *428
- Staphylococcal meningitis in the dog, bacitracin therapy of experimental, bacitracin levels in the cerebrospinal fluid after parenteral injections, (P. Teng and F. L. Meleney), ^{ab}439
- Stefanini, Mario, Recent advances in the theory of the mechanism of blood coagulation, *619
- Recent observations on the pathogenetic mechanism of idiopathic thrombocytopenic purpura, *452
- Stenosis, postoperative anal, (R. Turell), ^{ab}434
- Steppacher, Lester G., see Pomeranz, Alfred A., *465
- Stilbamidine and 2-hydroxystilbamidine in urine and tissue, quantitative determination of, (F. Lieben and I. Snapper), ^{ab}534
- Stomach, Hodgkin's disease involving the, ^{ab}612
- Streptomycin, aerosol, treatment of advanced pulmonary tuberculosis in children, (J. B. Miller, et al.), ^{ab}697
- Studies in pancreatic function. II—a statistical study of pancreatic secretion following secretin in patients without pancreatic disease, (D. A. Dreiling and F. Hollander), ^{ab}695
- in basic amines in the blood under physiologic and pathologic conditions, (Kurt Elias and Herbert Elias), ^{ab}614
- Successful removal of a tumor embolus from the femoral artery, (L. Blum), ^{ab}441
- Suggested modification for obstetrical forceps to avoid trauma, (Emanuel M. Greenberg), ^{ab}533
- Sulfadiazine and sulfamerazine in combined sulfonamide therapy, (Thomas G. Kantor), ^{ab}534
- Summary of experimental evidence relating life stress to diabetes mellitus, *537
- Surgical complications of congenital anomalies of the umbilical region, (E. E. Aruheim), ^{ab}689
- complications, rhinoplasty, and how to avoid them, (I. B. Goldman), ^{ab}435
- treatment of hernia in the aged, (Frank P. Sainburg), ^{ab}693
- Synthesis and properties of spiranes containing oxygen heterocycles, (J. D. Chanley), ^{ab}528
- T**ECHNIC for measuring cardiac output directly by cannulation of the pulmonary artery, (R. D. Seely and E. E. Gregg), ^{ab}433
- Temporal bone, the carotid canal as a pathway for extension of infection in the temporal bone, (J. G. Druss), ^{ab}435
- Testosterone, endometriosis of the large bowel treated with, (R. H. Marshak and A. I. Friedman), ^{ab}530

- Theoretical and practical aspects of the use of folic acid antagonists in human neoplasia, *583
- Therapy of ragweed hay fever with electrophoretically isolated fractions (artefolin and trifidin), preliminary report, (H. A. Abramson, et al.), ^{ab}698
- Thermophily, the dynamic nature of, (Mary Belle Allen), ^{ab}528
- Thrombocytopenic purpura, idiopathic, recent observations on the pathogenetic mechanism of, *452
- purpura, with hepatic dysfunction, and isolated peripheral nerve palsy, infectious mononucleosis, (R. S. Wallerstein and L. Madison), ^{ab}618
- Thymus gland, persistent cervical, thymectomy, (E. E. Arnheim and B. L. Genson), ^{ab}440
- Toe, human, in normal subjects and in patients with residua of trench foot and frostbite, quantitative blood flow measured calorimetrically in the, (Milton Mendlowitz and Harold A. Abel), ^{ab}431
- Toxicity of eugenol: determination of LD50 on rats, (H. A. Sober, et al.), ^{ab}431
- of the mucigogue, eugenol, administered by stomach tube to dogs, (F. U. Lauber and F. Hollander), ^{ab}691
- Transmesenteric hernia, *465
- Treatment of disseminated lupus erythematosus with cortisone and adrenocorticotropin, (G. Baehr and L. J. Soffer), ^{ab}440
- of heart failure: digitalis and mercurial intoxication, penicillin, dicumarol, major surgery, (A. M. Master, et al.), ^{ab}438
- Tricuspid valves, congenital atresia of pulmonary and, (S. K. Elster), ^{ab}529
- Trifacial (trigeminal) neuralgia with emphasis on atypical forms, *596
- Trypsin, pepsin and, use of dried bovine hemoglobin powder in the Anson and Mirsky methods for, (D. Orringer, et al.), ^{ab}431
- Tuberculosis in children, aerosol streptomycin treatment of advanced pulmonary, (J. B. Miller, et al.), ^{ab}697
- Tumor embolus from the femoral artery, successful removal of a, (L. Blum), ^{ab}441
- Turner, Louis B., The extracellular compartment: a comparison of the chloride and inulin spaces, *653
- Two-step exercise electrocardiogram: a test for coronary insufficiency, (A. M. Master), ^{ab}535
- exercise electrocardiogram in functional heart disturbances and in organic heart disease: the use of ergotamine tartrate, (A. M. Master, et al.), ^{ab}530
- exercise and anoxemia tests, (A. M. Master), ^{ab}612
- test, anoxic effects on the electrocardiogram produced by the, (A. M. Master), ^{ab}615
- Tympanic plexus, an anatomic study, (Samuel Rosen), ^{ab}693
- U**LTIMATE fate of the graft, (Herbert M. Katzin), ^{ab}437
- Umbilical region, surgical complications of congenital anomalies of the, (E. E. Arnheim), ^{ab}689
- Unusual sensitivity reaction to penicillin—report of a case with autopsy findings, (Robert M. Berne), ^{ab}533
- Urine and tissue, quantitative determination of stilbamidine and 2-hydroxystilbamidine in, (F. Lieben and I. Snapper), ^{ab}534
- blood and, fluorophotometric estimation of aureomycin in, (A. Saltzman), ^{ab}431
- Use of anticoagulant (dicumarol) in preventing post-irradiation tissue changes in the human lung, preliminary report, (S. H. Macht and H. J. Perlberg), ^{ab}437
- Uses of radioactive isotopes in medicine, (L. R. Wasserman and R. Loevinger), ^{ab}531
- V**AGOTOMY, series of peptic ulcer cases treated by, correlation of insulin test studies and clinical results in a, (V. Weinstein, et al.), ^{ab}434
- Variability of the electrocardiogram in congenital tricuspid atresia, (I. G. Kroop and A. Grishman), ^{ab}695
- Varicose veins, recent trends in the diagnosis and treatment of, (R. S. Nabatoff), ^{ab}616
- Ventricular contraction in Wolff-Parkinson-White syndrome: an electrokymographic study, (S. Dack, et al.), ^{ab}442
- Vertebrae in the aged, fractures of, (E. M. Bick), ^{ab}440
- Vertebra, the osteohistology of the normal human, its relation to scoliosis and certain lesions incident to growth and senescence, *490
- Viral diseases, newer methods in the diagnosis of, (A. L. Florman), ^{ab}435
- Visamin (khellin), observations on the clinical use of, (R. H. Rosenman, et al.), ^{ab}612
- Visualization of the coronary circulation during angiocardiology, (Alvin J. Gordon, et al.), ^{ab}430
- Vitamin C deficiency on the diffusion of T-1824 across the capillary wall, effect of, (S. K. Elster and J. A. Schack), ^{ab}534
- E administration upon diabetes mellitus, the effects of, (H. Pollack, et al.), ^{ab}616
- W**ARREN, Shields, The William Henry Welch lecture, the early changes caused by radiation, *443
- Wein, Stanley L., see Salzmann, J. A., *668

- Weiss, Paul, Medicine and society: the biological foundations, *716
- Weakness of extensor muscles of the wrist: an early sign in hemiparesis, (I. Strauss), ^{ab}439
- What is new in proctology, (Robert Turell and Albert S. Lyons), ^{ab}613
- William Henry Welch lecture, the early changes caused by radiation, *443
- lecture: from clostridium welchii to the coxsackie viruses: changing microbiology, *396
- Wolff-Parkinson-White syndrome, ventricular contraction in, an electrokymographic study, (S. Dack, et al.), ^{ab}442
- Wolf, Stewart, see Hinkel, Lawrence E., Jr., *537
- Wrist, weakness of the extensor muscles of the, an early sign in hemiparesis, (I. Strauss), ^{ab}439

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